Dissertation on

"A CASE-CONTROL STUDY ON SERUM PROTEIN, CHOLESTEROL AND HDL LEVELS IN PULMONARY TUBERCULOSIS PATIENT"

Submitted in partial fulfillment for the Degree of

M.D GENERAL MEDICINE

BRANCH – I

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CERTIFICATE

This is to certify that the dissertation titled **"A CASE-CONTROL STUDY ON SERUM PROTEIN, CHOLESTEROL AND HDL IN PULMONARY TUBERCULOSIS PATIENTS"** is the bonafide original work done by **DR. TEENA.K**, post graduate student, Institute of Internal medicine, Madras medical college, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch -1 General Medicine, under our guidance and supervision, during the academic year 2015-2018.

Prof. Dr.S.MAYILVAHANAN M.D.,
Director & Professor,
Institute of Internal Medicine,
Madras Medical College &
RGGGH, Chennai – 600003.

Prof. Dr. .R.PENCHALAIAH, M.D.,
Professor of Medicine,
Institute of Internal Medicine,
Madras Medical College &
RGGGH, Chennai – 600003.

Prof. Dr. NARAYANA BABU, M.D., DCH.
DEAN,
Madras Medical College & Rajiv Gandhi Government General Hospital,
Chennai 600 003.

DECLARATION

I, **Dr. TEENA.K** solemnly declare that dissertation titled "**A CASE-CONTROL STUDY ON SERUM PROTEIN, CHOLESTEROL AND HDL LEVELS IN PULMONARY TUBERCULOSIS PATIENT**" is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during March 2017 to August 2017 under the guidance and supervision of my unit chief **Prof. Dr. R.PENCHALAIAH M.D**, Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamil Nadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH-I**.

Place: Chennai -03
Date:

Dr. TEENA.K
MD General Medicine,
Post Graduate,
Institute of Internal Medicine,
Madras Medical College,
Chennai – 03

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ABBREVIATIONS

TB	- Tuberculosis
SIADH	- Syndrome of inappropriate antidiuretic hormone secretion
ESR	- Erythrocyte sidementation rate
ARDS	- Acute respiratory distress syndrome
AFB	- Acid fast bacilli
ATT	- Anti-tuberculous drug
TC	- Total count
CSF	- Cerebrospinal fluid
CBNAAT	- Cartridge-based nucleic acid amplification test
MTB/Rif	- Mycobacterium tuberculosis/ Rifampicin
INH	- Isoniazid
NAAT-TB	- Nucleic acid amplication test
BCG	- Bacille Calmette Guerin
TST	- Tuberculin skin test
IGRA	-Interferon Gamma release assay
ESAT-6	- Early secretory antigenic target 6kDa
CFP	- Culture filtrate protein 10
LPA	- Line probe assay
CXR	- Chest X-ray

PMDT	- Programmatic management of drug-resistent tuberculosis
EPTB	- Extrapulmonary tuberculosis
IP	- Intensive phase
CP	- Continuation phase
MDR	- Multi drug resistant
RR TB	- Rifampicin resistant tuberculosis
BDQ	- Bedaquiline

CONTENTS

Introduction

INTRODUCTION

TB has existed for millennium and remains a major global health problem. TB is one of the top 10 causes of death worldwide[1]. With India leading in percentage of TB affected people.

Malnutrition and tuberculosis are synergistically associated with each other. Infection with bacilli does not necessarily lead to active disease as the immune response of most individual can successfully contain the infection.

Action TB is acute inflammatory condition associated with increased generation of free radicals that have destructive effect on serum lipids (by means of lipid peroxidation) and also contribute to immune suppression.

Lipid are important constituent that determine nutritional status and the same time participate in immune function. Cholesterol constitute 30% of lipid content of plasma membrane and affects its fluidity. Phagocytic cells like macrophages require cholesterol for cell motility, exocytosis and endocytosis. Hypocholesterolemic patients had significantly lower levels of lymphocytes, T-cells, helper T-cells, CD8+ cells than hyper-cholesterolemic people.

It is well established that changes in serum protein occur in response to both acute and chronic infection. In pulmonary TB biochemical abnormality such as low serum albumin, increased bilirubin and ALP are common. Though hypoalbuminemia is not of diagnostic value, they do indicate the severity of infection. With albumin level decrease as the severity of disease increases.

Hypoalbuminemia and hypocholesterolemia have shown to improve with treatment and correlate well with recovery from the infection.

Aims and objectives

AIMS AND OBJECTIVES

- To study the prevalence of hypoalbuminemia and hypocholesterolemia in newly diagnosed pulmonary tuberculosis patients

Review of literature

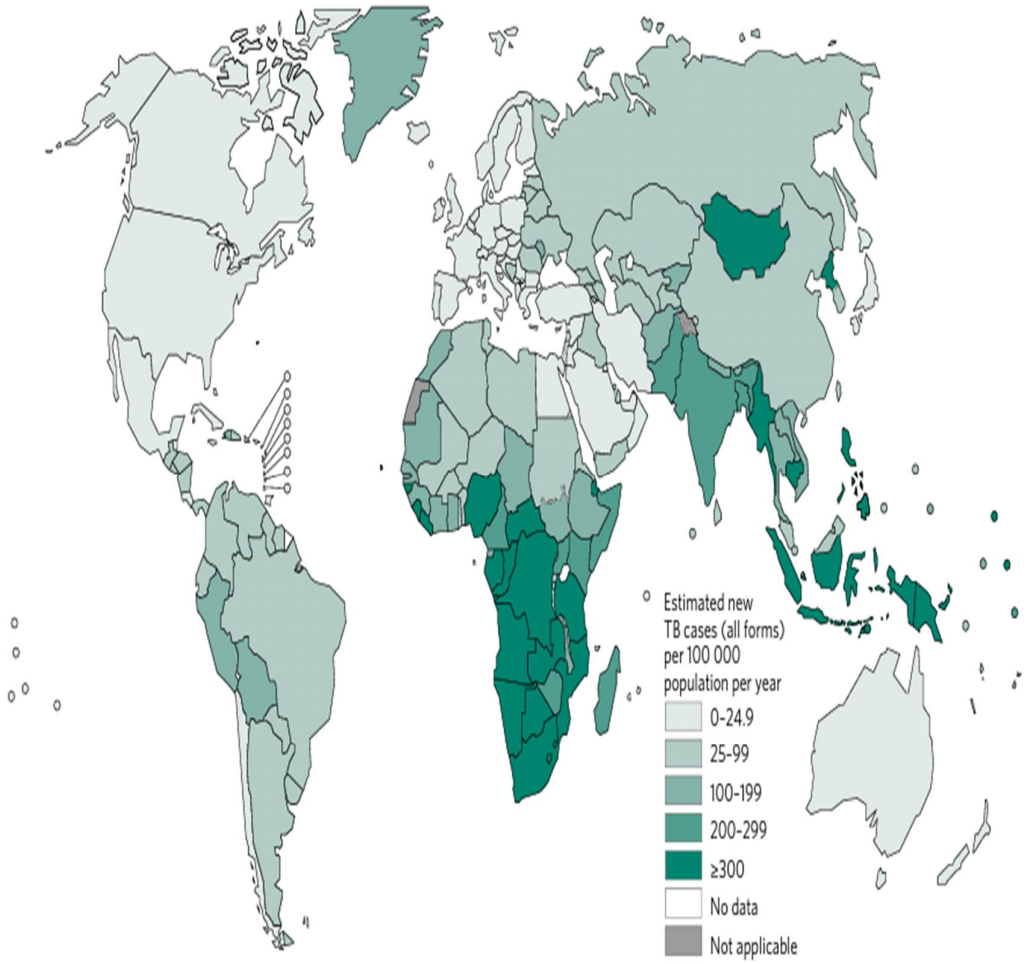
REVIEW OF LITERATURE

Tuberculosis has existed for a millennium. It is top 10 cause of death worldwide. An estimate of 1.4 million deaths worldwide due to TB and an estimate of 0.4 million death in TB patients with HIV. There has been 10.4 million new TB case in which 1.2 million been in HIV infected people . 5.9 million men, 3.5 million women and 1 million children[1,2]. Male to female ratio is 1.6:1.

Prevalence of TB is more among those living in overcrowded place, those who are malnourished and homeless. Its incidence has increased among HIV-positive individuals. In addition to high prevalence among HIV infected people, drug resistance is posing a major problem in disease control and treatment. The various genus of the mycobacteria which cause infection possess virulence factors like ESAT-6 and CFP-10.

Infection in persons with normal immune response leads on to granuloma formation.

Estimated TB incidence rates, 2015



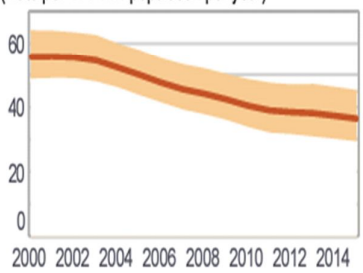
India

Tuberculosis profile

Population 2015 **1 311 million**

Estimates of TB burden*, 2015	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	480 (380 590)	36 (29 45)
Mortality (HIV+TB only)	37 (21 57)	2.8 (1.6 4.3)
Incidence (includes HIV+TB)	2 840 (1 470 4 650)	217 (112 355)
Incidence (HIV+TB only)	113 (58 186)	8.6 (4.4 14)
Incidence (MDR/RR-TB)**	130 (88 180)	9.9 (6.7 14)

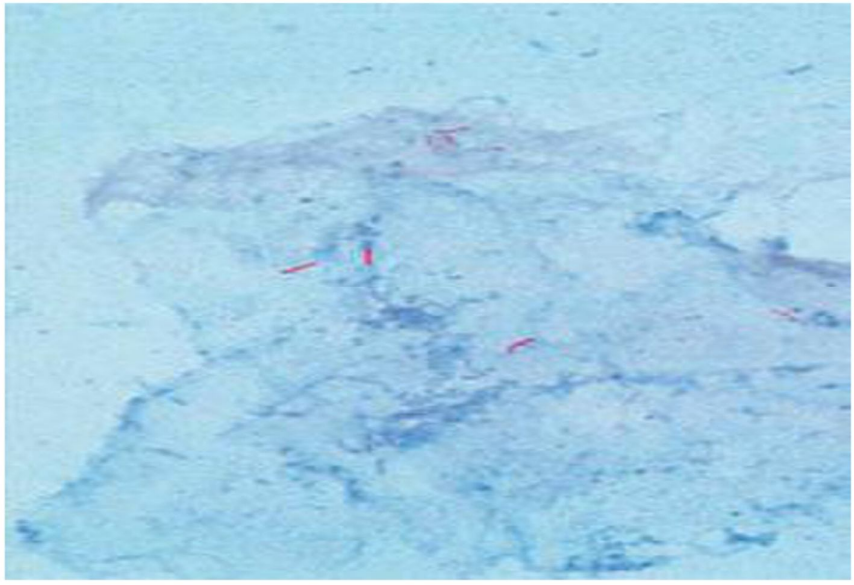
(Rate per 100 000 population per year)



Prevalence of TB in INDIA[1]

Mycobacterium tuberculosis had emerged about 70,000 years ago in Africa. Disease mostly affects the lungs though other organs can be involved in one third of cases[5]. Disease is fatal in 50 to 60% of patients in 5 years time if untreated. Transmission is by spread by droplet nuclei from infected person[6,7].

Tuberculosis is caused by any one of three mycobacterial pathogens that are part of the M. tuberculosis complex: M. tuberculosis, Mycobacterium bovis, and Mycobacterium africanum[8,9]. The other members of the M. tuberculosis complex are: Mycobacterium microti, Mycobacterium pinnipedii, and Mycobacterium caprae, which only rarely cause disease in humans[10].



Mycobacterium tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring 0.5 micro m by 3 micro m. In addition to being acid fast, the mycobacterium are primarily intracellular pathogens, are obligate aerobes, and, in the presence of a normal immune response, induce a granulomatous response in tissue.

RISK FACTORS FOR ACTIVE TUBERCULOSIS IN PERSONS INFECTED WITH TUBERCLE BACILLI

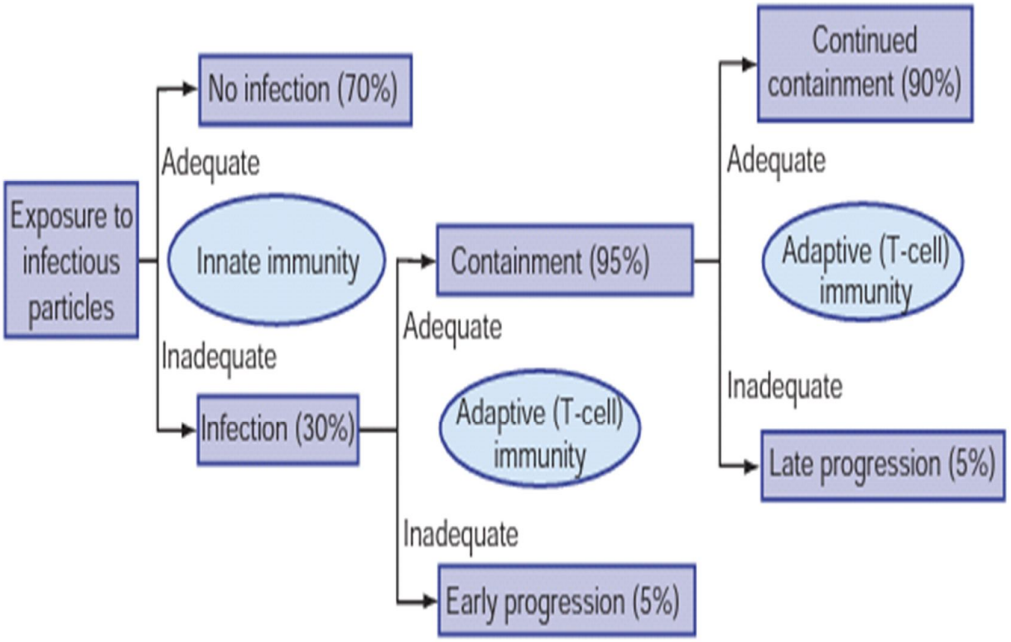
Risk Factors	Relative Risk
HIV infection	100
Jejuno-ileal bypass	30 to 60
Silicosis	30
Post-organ transplantation status	20 to 70
Recent TB infection (< 1 year)	13
Intravenous drug use	10 to 30
Chronic renal failure/haemodialysis	10 to 25
Immunosuppressive/corticosteroid therapy	10
Gastrectomy	2 to 5
Diabetes mellitus	2 to 4
Malnutrition	2

TB = Tuberculosis; HIV = Human immunodeficiency virus.

PATHOGENESIS

Inhalation of the tubercle bacilli through airborne droplet infection reaches the aveoli. There they are engulfed by macrophages. Those who escape this immune response lead on to infection witth hematogenous and lymphatic spread, before the development of effective immune response.

This stage , primary tuberculosis , is clinically and radiologically silent in most of the patients (usually). But in those with inadequate immune response, to contain this infection go on to develop progressive primary tuberculosis. Persons with intact T-cell, cell mediated immunity limit the multplication of TB bacilli by granuloma formation, thus preventing the spread. This latent tuberculous infection may reactivate aprox 6% of individual when host defences are impaired, leading on to active infection. There is no clinical feature that can differentiate primary from latent infection, though it is believed that 90% of TB in adukts is due to activation of latent infection.



Consequences of exposure to an infectious source case of tuberculosis depending on the status of immunity. Exposure to a patient with infectious tuberculosis causes tuberculous infection in approximately 30% of those exposed. Of those who are infected, 3% to 10% develop tuberculosis within 1 year of their becoming infected. Beyond 1 year, an additional 3% to 5% develop tuberculosis during the remainder of their lifetimes[3,11].

CLINICAL MANIFESTATION:

Pulmonary TB

Pulmonary TB is categorized as primary or post-primary (adult-type, secondary). Adult pulmonary TB is due to recent infection (either primary infection or re-infection) and not from reactivation.

Primary Disease:

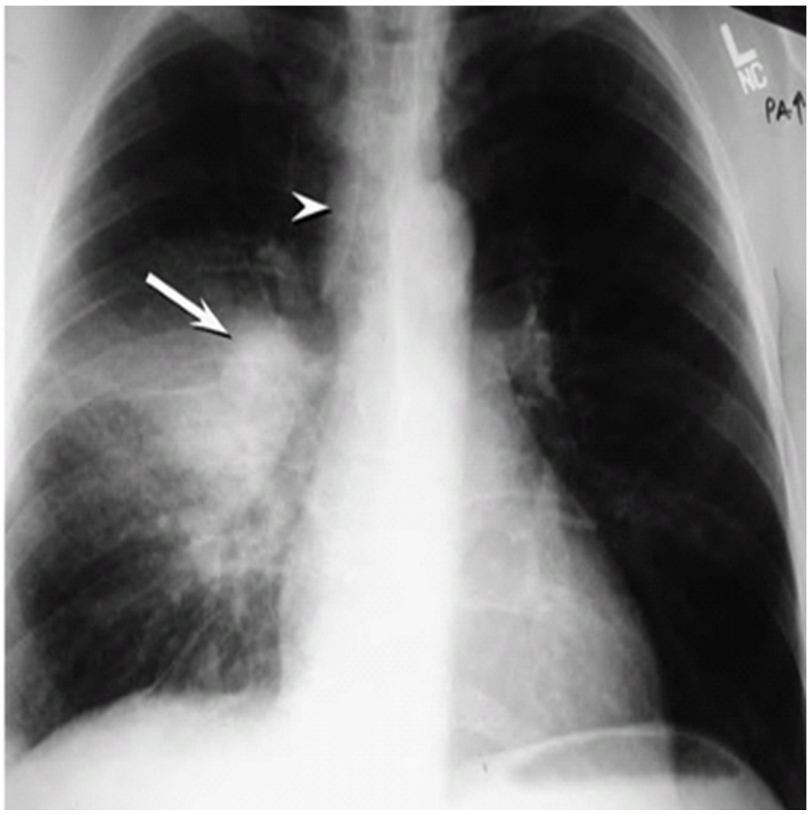
Primary pulmonary TB occurs after initial infection with tubercle bacilli. Infection may be asymptomatic or may present with fever and occasional pleuritic chest pain. In areas of high TB transmission, this form of disease mostly seen in children. Since most inspired air is distributed to the middle and lower lung zones, these regions are commonly affected in primary TB[7].

The lesion after initial infection called Ghon focus is usually peripheral and accompanied by transient hilar or paratracheal lymphadenopathy, which may or may not be visible on chest X-ray. Some develop erythema nodosum or phlyctenular conjunctivitis. In the majority of infected cases, the lesion heals spontaneously evident only as residual calcified nodule. Pleural reaction in sub pleural infection is common. The Ghon focus, with or without overlying pleural reaction, thickening, and regional lymphadenopathy, is known as Ghon complex

In young children with immature cell mediated immunity and in those with impaired immunity due to malnourishment or HIV infection, primary pulmonary TB will progress rapidly.

Primary TB may present as pleural effusion in two third of cases due spread of TB bacilli to pleural space from sub pleural focus. Enlarged lymph node may compress the bronchi to cause wheeze by partial obstruction, or distal collapse with total obstruction. Rupture of node in bronchi lead on to pneumonia. Bronchiectasis may develop in any lobe or segment as a result of progressive caseating pneumonia.

The primary site may enlarge rapidly in severe cases where its central portion undergoes necrosis resulting in cavity formation (progressive primary TB). In young children hilar or paratracheal lymphadenopathy occur due to spread of bacilli from lung parenchyma to lymphatic vessels.



Frontal chest radiograph in a young adult shows superior segment right lower lobe consolidation associated with right hilar lymphadenopathy (arrow) due to primary Mycobacterium tuberculosis infection. Mild right paratracheal lymph node enlargement (arrowhead) is also visible.

Disseminated or miliary spread of primary infection can occur to other organs in the absence of sufficient acquired immune response. TB meningitis is particular concern in children and HIV infected.

POSTPRIMARY DISEASE : Adult type

Known as reactivation or secondary TB, post-primary TB is most accurately termed adult-type TB as it may result from endogenous reactivation of distant latent TB infection or from primary infection or re-infection. Since high mean oxygen tension is present(which favours mycobacterium growth) in apical and posterior segments of the upper lobes compared with that of lower zones, lesion is most commonly seen in this region.. The superior segments of the lower lobes are also frequently involved.

The lung parenchymal involvement may vary from small infiltrate to cavitation. In cavitation the liquefied necrotic contents may discharge into the airways and undergo bronchogenic spread, resulting in satellite lesions within the lungs that may result in cavity formation. Massive involvement of pulmonary segments or lobes, will result in caseating pneumonia.

One third of non treated patient succumb to infection in few months known galloping lesion others might go in for cure or chronic progressive debilitating illness (“consumption” or phthisis). These may undergo fibrosis and may calcify, but cavities may persist in other parts. Persons with such chronic diseases will spread tubercle bacilli for long time.

Usually patients present with fever with evening rise of temperature, loss of weight, fatigue, chronic cough which may initially be non productive later on becomes muco-purulent with or without hemoptysis. Hemoptysis may develop in 20 to 30 percent, massive amount may be due to rupture of blood vessel.

Extensive lung parenchymal involvement will cause dyspnea and rarely may lead on to ARDS. On auscultation patient has inspiratory rales, particularly after coughing. Patient may have anemia, clubbing and haematology wise leukocytosis, thrombocytosis and elevated ESR. C-reactive protein may be elevated. Hyponatremia may occur due SIADH.

EXTRAPUMONARY TB:

In descending order of frequency, the extrapulmonary sites most commonly involved are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium.

Lymph node

It is most common form of extra pulmonary TB in both HIV infected and non HIV infected patients. Incidence is more in children and HIV positive persons. Posterior cervical and supraclavicular nodes are more commonly involved. They present usually as discrete non-tender node which later coalesce and get matted, later on leading to fistula formation.

Diagnosis is by fine needle aspiration or by excision biopsy. Smear is positive for AFB or culture is positive in 80% of patients[13]. Histopathalogic examination shows granulomatous caseating lesion. HIV seropositive persons have high load of AFB bacilli in both smear and culture, in these patients granuloma is poorly formed or absent[14].

Corticosteroid treatment has been used to shrink intra-thoracic nodes and relieve bronchial obstruction, primarily in children. Although rare, upper airway obstruction may result from cervical node enlargement. Both chylous pleural effusion and ascites have resulted from intra-thoracic or abdominal node involvement with obstruction of retroperitoneal lymphatics or the thoracic duct.

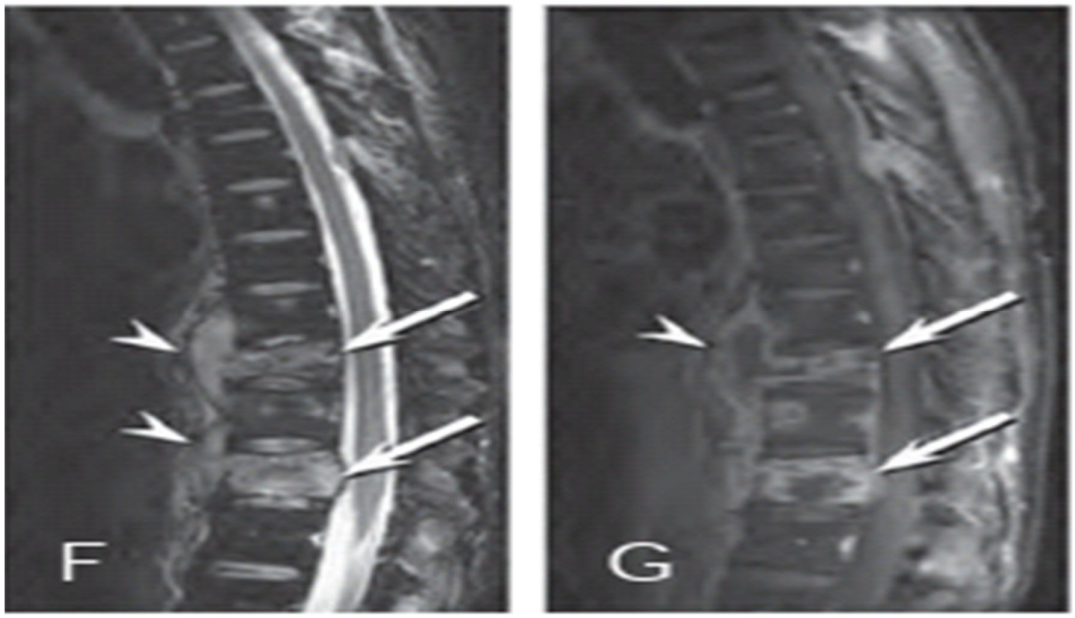
Skeletal Tuberculosis:

It accounts for 10% of extra pulmonary tuberculosis. Spine involvement upto 50%, knee and hip upto 15%, other bone and joint upto 15 to 20%[17]. Spine it affects 2 or more adjacent vertebral bodies. Upper thoracic spine is more involved in children compared to lower thoracic and lumbar spine in adults.

Pathogenesis is reactivation of hematogenous foci from initial bacillemia or spread from adjacent paravertebral lymph nodes. Evidence of either previous or current pulmonary TB is found in approx half of the patients reported.

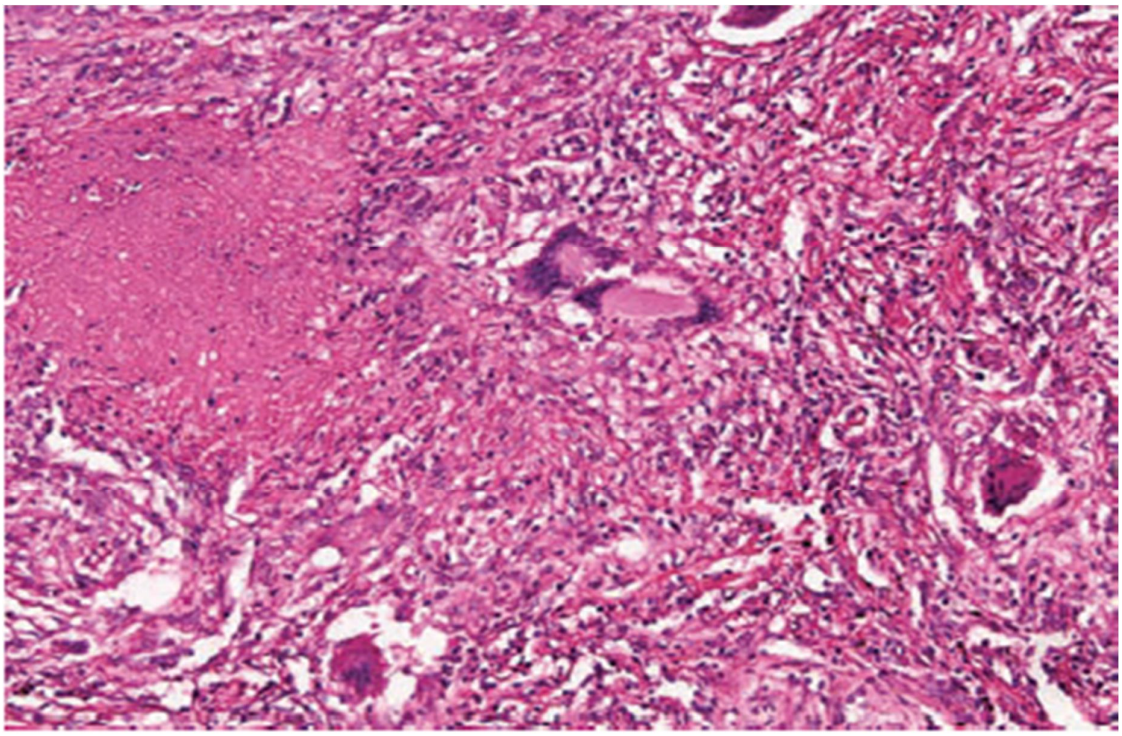
Spine involvement present as paraparesis either due to large abscess or tuberculoma or caries spine. Large abscess need urgent surgical drainage. Advanced disease lead on to spine deformity inform of Gibbus.

CT and MRI imaging shows characteristic bony lesion. Confirmation require synovial fluid aspiration and staining and culture. Synovial biopsy and tissue culture may also be required. Evidence of granulomatous inflammation do support the diagnosis.



Saggital T2 weighted and contrast enhanced T 1 weighted images shows anterior paraspinous abscesses typical of subligamental spread. Relative sparing of intervertebral disc space, typical of granulomatous infection.

Surgical intervention is usually not required[16]. Treatment with ATT with prolonged period of 6 to 9 month needed as follow up of bacteriological clearance is difficult[15].



Tuberculous granuloma with caseation, lymphocytes, epitheloid cells and Langhans gaint cells

Genitourinary TB:

Seeding of kidney occurs during initial infection and bacillemia. In 90% bilateral kidney is affected[18]. Genital TB may be associated with renal involvement or by a hematogenous spread without renal involvement in 11%.

Symptoms include pyuria, hematuria, flank pain, and infertility in women and men present as scrotal swelling[19]. Confirmation is by urine AFB and culture of morning first voided urine (3 samples) . Isolated genital involvement requires biopsy for confirmation and to rule out other cause.

Pleural TB:

20 % of extra pulmonary case. Collection of fluid reflect spread of bacilli leading on to hypersensitivity reaction to TB bacillus antigen in presence of cell mediated immunity[20]. It may resolve spontaneously even without treatment.

Pleural fluid analysis shows >50% of protein that of serum, normal or low glucose, ph=7.3 and TC of 100 to 5000 cells mostly lymphocytes[21]. AFB is rarely seen in smear and culture. ADA, lysozyme and interferon gamma can be tested. Needle biopsy of pleura may be required which is highly specific and sensitive.

Another form is due to rupture of cavity in pleural space leading onto empyema formation. Bronchopleural fistula also may occur. Pleural fluid AFB is strongly positive along with culture. It contains cholesterol which may mimic chylous effusion hence called pseudo chylous effusion.

Treatment with ATT and glucocorticoids as a adjuvant. Surgical drainage is required may be for long period of time.

Central Nervous system:

It accounts for 5 % of extra pulmonary TB**.** Incidence is mor common among children and HIV seropositive individual**.** Infection may occur by hematogenous spread from primary or post primary infection or also due to rupture of subependymal tubercle into subarachnoid space[22]. It evolves over 1-2 weeks, presenting as fever, malaise, headache, seizures and neck stiffness. Most of them have old pulmonary healed lesion or miliary pattern on chest X-Ray.

CSF analysis shows high leukocyte count 100 to 1000cells/microL[23], with predominant lymphocytes, with high protein of 100 to 800 mg/ dl and low sugar. AFB is not frequently seen but culture turn out to be positive in 80% of cases. Gene xpert is preferred initial investigation and has 80% sensitivity. Though there is response to treatment some25% of patients have neurological sequelae. If untreated it has high mortality.

Gastrointestinal TB:

It is uncommon of the extra pulmonary TB. TB peritonitis occurs due to rupture of lymph node or due to spread from nearby organ. Most common site of involvement is terminal ileum and caecum[24]. Confirmation mostly needs tissue biopsy. Spread occurs due to hematogenous seeding, swallowing of sputum and drinking of infected milk (bovine).

PERICARDIAL TB:

Direct extension of an adjacent focus of disease from the lung parenchyma, pleura, or tracheobronchial lymph nodes into the pericardium. Also can occur by initial bacillemia, manifesting after period of quiescence. It is likely that hypersensitivity plays a role in producing the intense inflammatory response and abundant effusion in the pericardium. Most instances the fluid accumulates slowly, the

pericardium can expand to accommodate large volumes (2 to 4 L) with little apparent hemodynamic compromise.

Tubercle bacilli have been identified in pericardial fluid in approximately 25% to 30% of cases (smear and culture combined)[25].Biopsy of the pericardium with both histological and bacteriological evaluation is more specific and sensitive[3].

Constriction occurs with chronic infection of 6 months. Fibrosis cause fusion of visceral and parietal pleura leading on to hemodynamic compromise. Hence anti-tuberculous treatment should be started early as the diagnosis is confirmed or there is stony suspicion of TB.

DISSEMINATED or MILIARY TB:

The term miliary is derived from the similarity of the lesions to millet seeds. Grossly, these lesions are 1- to 2-mm yellowish nodules that on histological examination are granulomas. In adults it may occur as reactivation of old foci or recent infection, in children mostly due to primary infection.

Radiographic abnormality occurs in 70-90%. Combinations of bronchoalveolar lavage and transbronchial biopsy has high yield[26]. Most potential sites for biopsy are liver and bone marrow, which is diagnostic of showing granulomas (70% to 80%)[27]. 25% to 40% provide bacteriologic confirmation; urine cultures are positive in 25% of patients[28].

HIV –associated TB

It is responsible for an estimated 24% mortality amoung HIV infected people, being the most common infection in this group of individuals worldwide. The annual risk of developing active TB in HIV infected persons with TST positive is about 3-14%. Unlike the general population new infection of TB in these persons lead on to active infection in weeks than in months or years, like in normal person.

At early stages when CD4 cells are not that much reduced TB infection is most commonly pulmonary, with upper lobe cavitation with significant effusion or lymph node enlargement. Though in later stages with reduced cell count, extra-pulmonary sites are more commonly affected, with pulmonary type showing atypical finding of lower lobe infiltrates, miliary distribution, effusion and lymphadenopathy. Infection does not lead on to classical granuloma formation with impaired cell mediated immunity.

Diagnosis is difficult in HIV infected TB patient in view of smear negativity and atypical radiological features. Sputum culture are gold standard test, Gene-xpert should be routinely done and is also the preferred first line investigation.

Treatment: several studies have shown good response rate in concomitant use of ATT and ART in HIV positive TB patients and also has reduced the mortality in these patients.

ATT is started first followed by initiation or continuation of ART within 2 weeks of ATT initiation. ART is indicated for HIV positive TB patients at any CD4 count. ART is to be initiated within 2 weeks of ATT at CD4 count of < 50 cells. ART should be a combination of two drugs nucleoside reverse transcriptase inhibitors and a nonnucleoside reverse transcriptase inhibitors. Rifampicin should not be combined with protease inhibitors, since rifampicin is a potent inducer of cytochrome P450 enzyme system.

COMPLICATION OF TB INFECTION

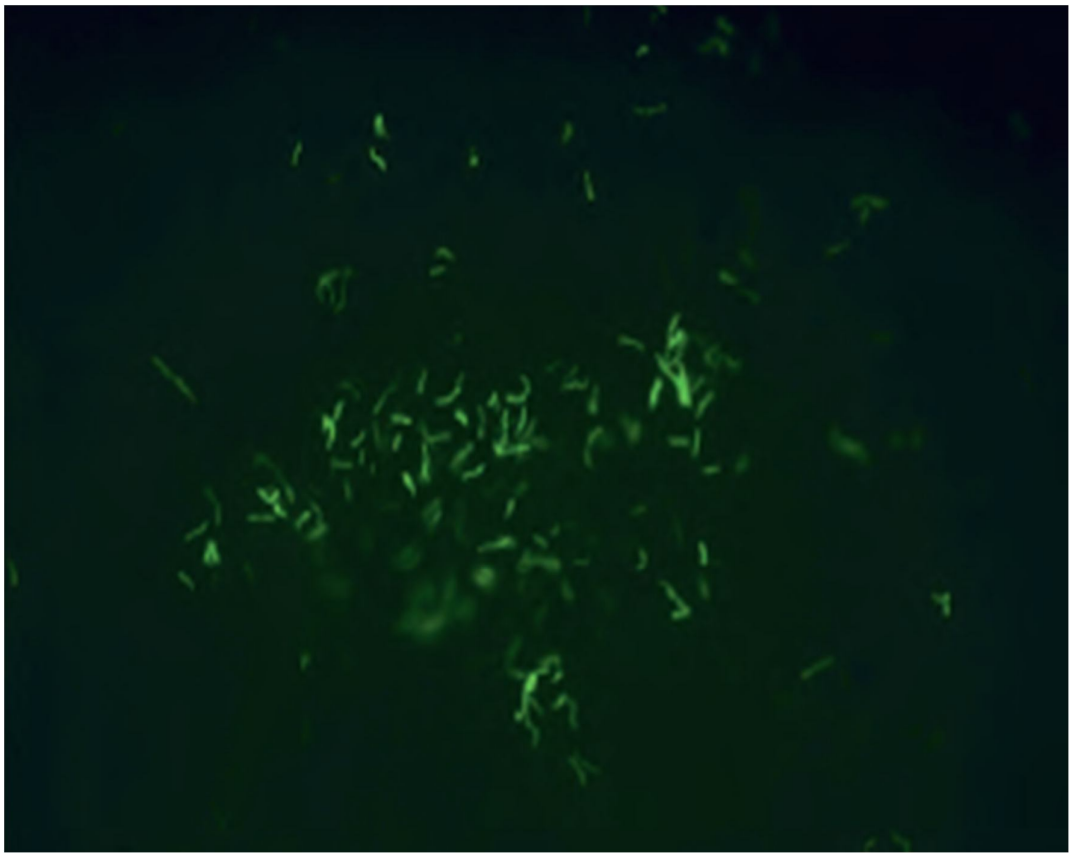
Pulmonary	Extra-pulmonary
Development of MDR-TB or XDR-TB	Disseminated TB
Miliary TB	Spread to extra-pulmonary sites, viz. central nervous system and meninges, bones and joints, lymph nodes, genitourinary system, gastrointestinal system, pericardium, skin
Massive haemoptysis	
Cor pulmonale	
Emphysema	
Chronic bronchitis	
Bronchiectasis	
Broncho-pleural fistula	Empyema necessitans
Lung/Pleural calcification	Laryngitis
Aspergilloma	Anorectal disease
Atypical mycobacterial infection	Amyloidosis
	Poncet's polyarthritis

DIAGNOSIS

1. Sputum smear microscopy (for AFB)
2. Culture
3. Rapid molecular diagnostic testing
    a. Line probe assay
    b. Cartridge Based Nucleic acid amplification test (CBNAAT) the GeneXpert system.
4. Radiography
5. Tuberculin skin testing

- Cartridge Based Nucleic Acid Amplification (CBNAAT) MTB/Rif testing using GeneXpert system.
- Line probe assay for MTB complex and detection of RIF & INH resistance
- WHO recommends the use of XpertMTB/RIF as the initial diagnostic test rather than microscopy ,culture and DST.

Auramine fluorochrome stain of sputum smear



DIAGNOSTIC METHODS IN TUBERCULOSIS

Test	Time to Result	Test Characteristics
Acid-fast bacilli light microscopy	1 day	Three morning specimens recommended. Combined sensitivity of 70% (54% for the first specimen, 11% for the second specimen, and 5% for the third specimen). First morning specimen increased yield by 12% compared to spot specimen.
Nucleic acid amplification test, detection (NAAT-TB)	1 day	Sensitivity/specificity high for smear-positive specimens, 85–97% for both, but sensitivity falls in smear-negative specimens to ~66%. Therefore, a positive NAAT in smear-negative patients with intermediate to high (> 30%) pretest probability of *M tuberculosis* infection is helpful while a negative NAAT is not. Should not be ordered in patients with low pretest probability of *M tuberculosis* infection.
Nucleic acid amplification test, resistance markers (NAAT-R)	1–2 days	Multiple assays for rifampin and isoniazid are available. Specificity uniformly high, > 98%. Sensitivity varies from about 84% to 96%, increases with multiple specimens. See text for indications for testing.
Mycobacterial growth detection Liquid (broth based) medium Solid (agar or egg based) medium	Up to 6–8 weeks Avg 10–14 days Avg 3–4 weeks	Liquid culture methods are more sensitive (~90% and 76%, respectively) with shorter time to detection but higher contamination with bacterial growth than solid culture methods. Specificity exceeds 99% for all methods.
Identification of *M tuberculosis* complex by DNA probe or high performance liquid chromatography	1 day[1]	May be useful in areas of low *M tuberculosis* incidence where nontuberculous mycobacteria are commonly isolated.
First-line drug susceptibility testing (liquid medium)	1–2 weeks[1]	Gold standard. Should be performed routinely on the initial isolate.
Second-line and novel compound drug susceptibility testing Liquid (broth based) medium Solid (agar or egg based) medium	 1–2 weeks[1] 3–4 weeks[1]	

Tuberculin skin test:

It is of limited value due to low sensitivity and specificity. It is usually used to diagnose latent tuberculosis infection. It is to antigenic response of T cells in skin. A standard tuberculin test involves intracutaneous injection of 0.1ml which contains 5 tuberculin units. The test is read at 48-72hrs after injection, but can be read even upto 1 week[30] , a correctly placed injection causes well-demarcated wheal of 6-10mm in diameter.

A reaction of more than 10mm is considered positive indicative of infection. The size of induration is important, than the amount of erythema(not taken into account).

A reaction of even 5mm is considered positive in HIV infected persons and in children in contact with smear positive tuberculosis and indicates tuberculous infection. Tuberculin reactivity is decreased in patients on corticosteroids and immunosuppressive drugs. A minimum dose of prednisone of 15 to 20 mg or a equivalent of another preparation, daily for 2 to 3 weeks[31]. Malnutrition and advancing age[32] diminish tuberculin reactivity.

It cannot differentiate between latent TB infection and active infection. False positive result is seen in BCG vaccination and in those with non mycobacterial infection. False negative in severe infection and in immunocomprimised individual

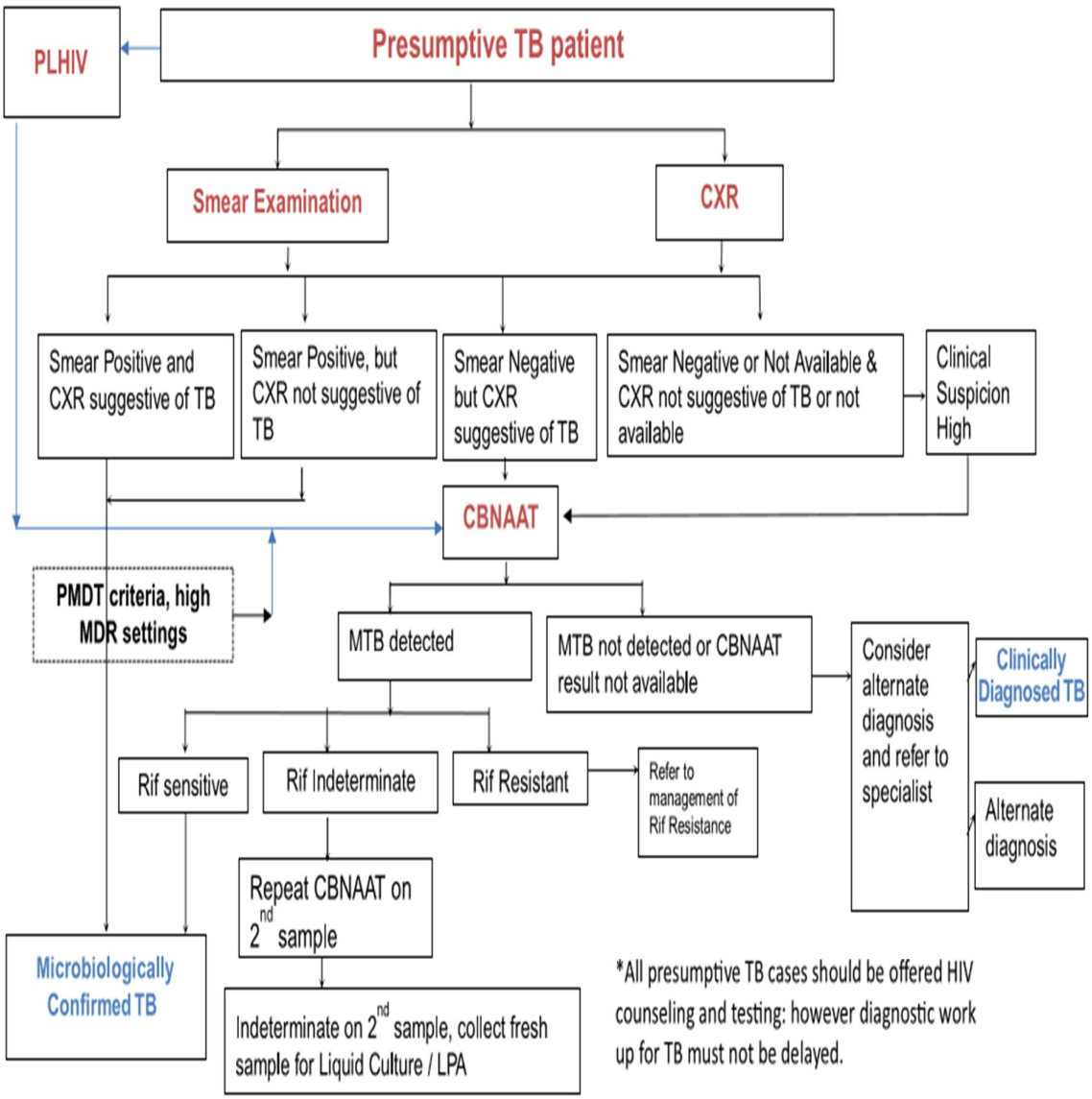
SIGNIFICANT TUBERCULIN TEST

Risk Group	Tuberculin Reaction Size, mm
HIV-infected persons	≥5
Recent contacts of a patient with TB	≥5[a]
Organ transplant recipients	≥5
Persons with fibrotic lesions consistent with old TB on chest radiography	≥5
Persons who are immunosuppressed, e.g., due to the use of glucocorticoids or tumor necrosis factor α inhibitors	≥5
Persons with high-risk medical conditions[b]	≥5
Recent immigrants (≤5 years) from high-prevalence countries	≥10
Injection drug users	≥10
Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settings[c]	≥10
Children <5 years of age; children and adolescents exposed to adults in high-risk categories	≥10
Low-risk persons[d]	≥15

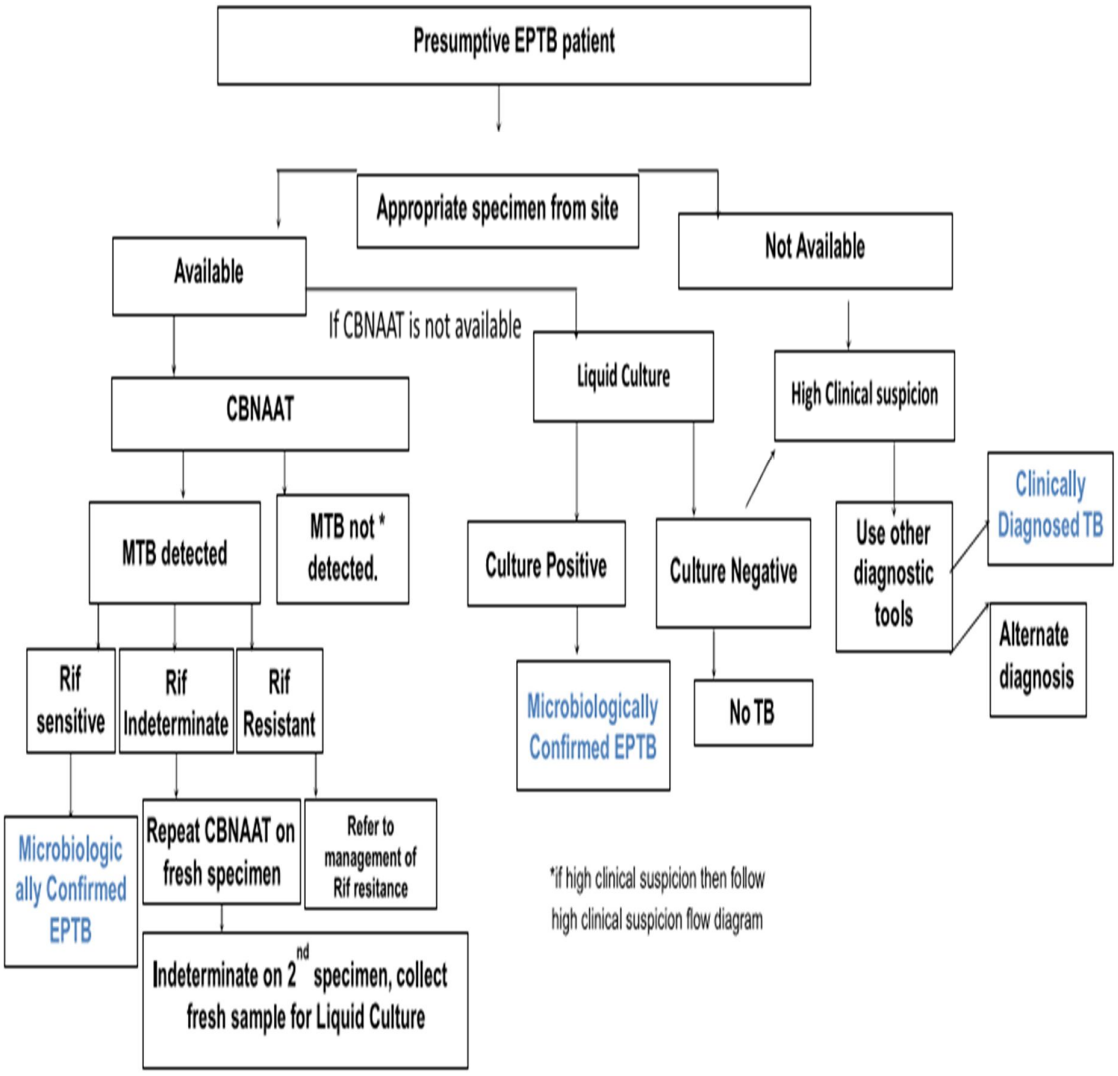
INF-gamma release assay:

Two in vitro assays that measure T cell release of IFN-γ in response to stimulation with the highly TB-specific antigens ESAT-6 and CFP-10 are available[29]. It is useful in population with low prevalence of TB and HIV. It is reaction of circulating memory T cells. Because of high cost WHO has recommended not to replace TST by IGRA in low and middle income countries. Two type of test is used currently , the QuantiFERON-TB test and T-SPOT.TB test[3]. T-SPOT.TB test is not affected by CD4 T-cell depletion[33]. Pai and colleagues have conducted study in India in 216 nursing and medical students with QFT-GIT test[34].

Diagnostic algorithm for pulmonary TB



Diagnostic Algorithm for Extra Pulmonary TB



ANTI-TUBERCULOUS DRUGS

GROUP 1	First line oral anti-TB drugs	Isoniazid,Rifampin,Pyrazinamide,Ethambutol
GROUP 2	Injectable anti-TB drugs	Streptomycin , Kanamycin, Amikacin,Capreomycin
GROUP 3	Fluoroquinolones	Ofloxacin,Levofloxacin,Moxifloxacin,Ciprofloxacin
GROUP 4	Second line oral anti-TB drugs	Ethionamide ,Prothionamide,Cycloserine, Terizidone,PAS
GROUP 5	Drugs with unclear efficacy	Thiacetazone, Clarithromycin, Clofazimine,Linezolid,Amoxicillin/clavulanate,Imipenem/cilastatin

TREATMENT REGIMEN

TREATMENT OF NEWLY DIAGNOSED AND PREVIOUSLY TREATED TB CASES

Type of TB cases	Treatment regimen in IP	Treatment regimen in CP
NEW	(2) HRZE	(4) HRE
PREVIOUSLY TREATED	(2) HRZES + (1) HRZE	(5) HRE

H- Isoniazid, R-Rifampicin, Z-Pyrizinamide, E-Ethambutol,

S-Sterptomycin inj.

Until now RNTCP had adopted thrice weekly guidelines for tuberculosis treatment. The programme is now introducing daily regimen treatment of drug sensitive tuberculosis in pediatric and in HIV patients, and also all TB patients in 104 districts initially[4]. Rast of the country will follow daily regimen until it is scaled up to daily regimen in entire country[4]. In daily regimen fixed dose combination of drug will be issued daily in appropriate weight bands.

The continuation phase in both New and Previously Treated Cases may be extended by **12 – 24 weeks** in certain forms of TB like

1. **CNS TB**
2. **Skeletal TB**
3. **Disseminated TB**

Based on clinical decision by the treating physician.

MDR/RR-TB cases

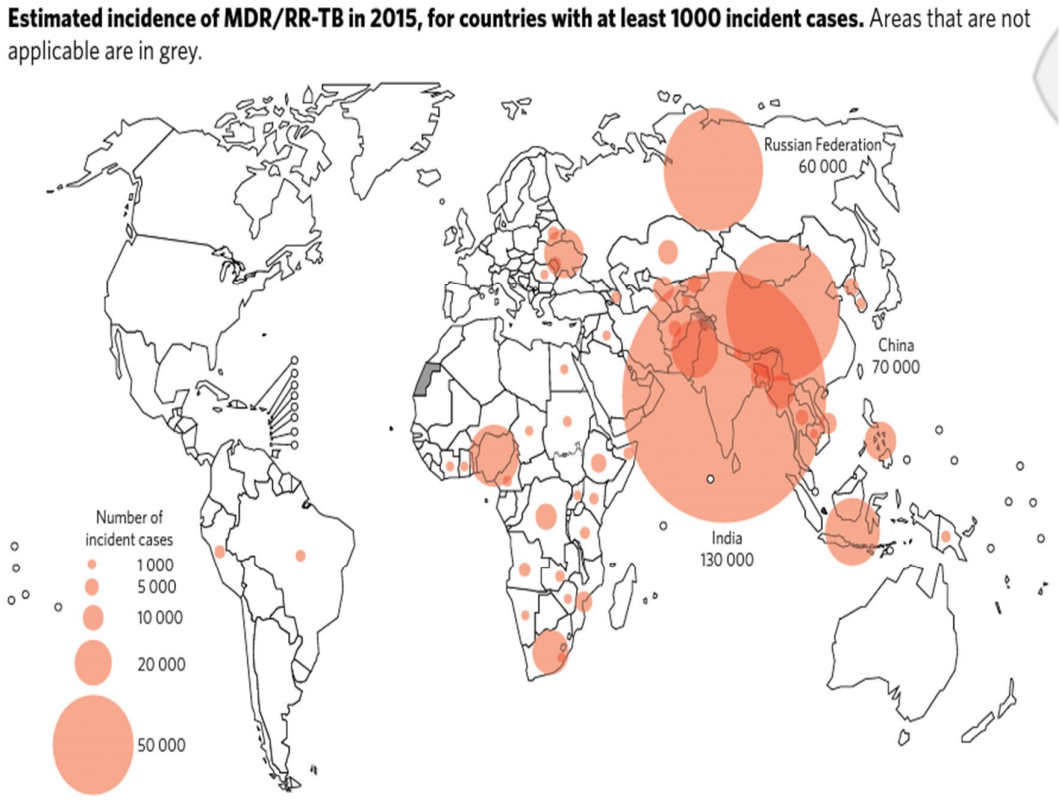
	Treatment regimen in IP	**Treatment regimen in CP**
Rifampicin resistant / INH sensitive or unknown	Km, Lfx, Eto, Cs, Z, E, H (6-9)	(18) Lfx, Eto, Cs, E, H
MDR TB	KM, Lfx, Eto, Cs, Z, E (6-9)	(18) Lfx, Eto, Cs, E

KM- Kanamycin , Lfx- Levofloxacin , E –Ethambutol , Eto- Ethionamide, Cs- Cycloserine , H – Isoniazid , Z – Pyrazinamide,

INH RESISTENCE[4]

- High level resistance by liquid culture-omit INH
- Low level resistance by liquid culture-add high dose INH
- If LPA reports INH resistance by KatG mutation – omit INH

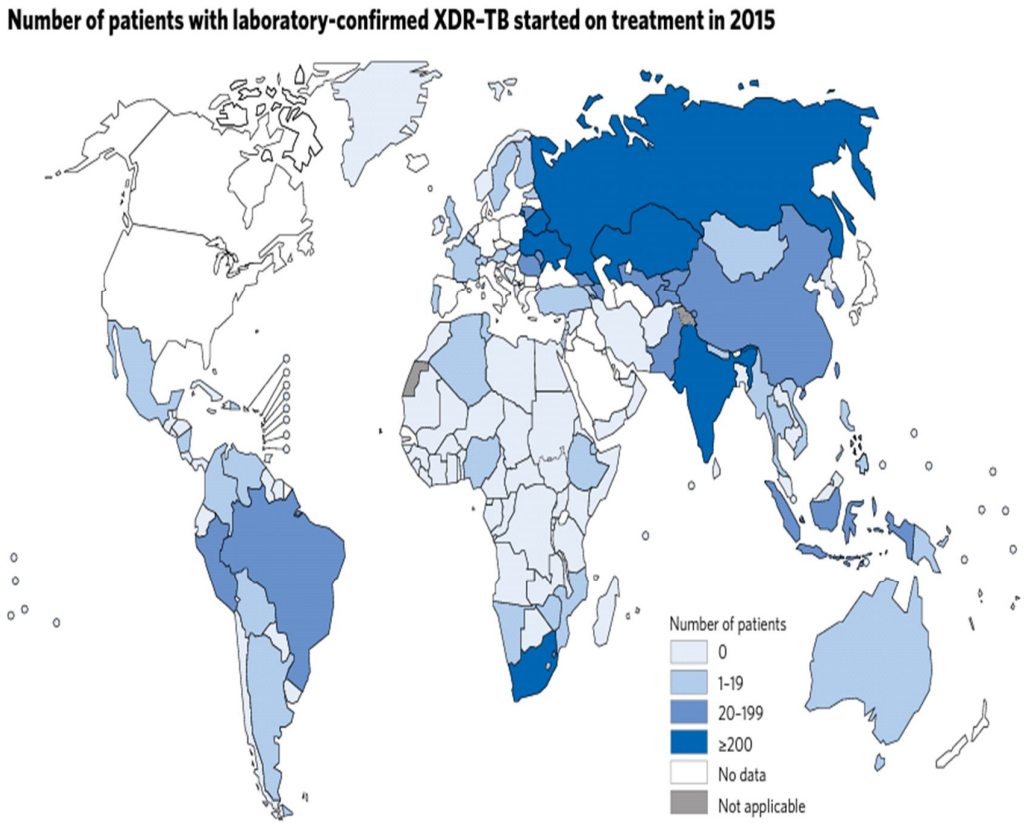
If LPA reports INH resistance by INH A mutation – use high dose INH. Ethionamide in the treatment regimen will be replaced with PAS



TREATMENT OF XDR-TB

	Treatment regimen in IP	Treatment regimen in CP
XDR	(6-12) Cm, PAS, Mfx, High dose-H, Cfx, Lzd, Amx/Clv	(18)PAS, Mfx, High dose H, Cfx, Lzd, Amx/Clv

Cm – Capreomycin, PAS – Para-Aminosalicylate Sodium, Mfx – Moxifloxacin, Lzd – Linezolid, Cfz – Clofazimine, H – Isoniazid, Amx/Clv - Amoxyclav



Dosage of ATT

Weight category	Intensive phase H R Z E 75/150/400/275	Continuation phase H R E 75/150/275	Inj.streptomycin gm
25 – 39 kg	2	2	0.5
40 – 54 kg	3	3	0.75
55-69 kg	4	4	1
> 70 kg	5	5	1

Body Weight (Kg)	Intensive Phase			Continuation Phase		
	Drugs	Dose (mg)	Duration	Drugs	Dose (mg)	Duration
16 to 25	Kanamycin Pyrazinamide Levofloxacin Ethambutol Ethionamide Cycloserine	500 500 500 400 375 250	6 to 9 months	Levofloxacin Ethambutol Ethionamide Cycloserine	500 400 375 250	18 months
26 to 45	Pyridoxine Kanamycin Pyrazinamide Levofloxacin Ethambutol Ethionamide Cycloserine	50 500 1250 750 800 500 500	6 to 9 months	Levofloxacin Ethambutol Ethionamide Cycloserine	750 800 500 500	18 months
>45	Kanamycin Pyrazinamide Levofloxacin Ethambutol Ethionamide Cycloserine	750 1500 750 1000 750 750	6 to 9 months	Levofloxacin Ethambutol Ethionamide Cycloserine	750 1000 750 750	18 months

MDR = Multidrug-resistant; TB = Tuberculosis; DOTS = Directly Observed Treatment Short-course; RNTCP = Revised National Tuberculosis Control programme.

SIDE EFFECT PROFILE OF FIRST LINE ATT

Side Effects	Drugs Probably Responsible	Management
Minor		Continue anti-TB drugs
Orange or red coloured urine	Rifampicin	Reassurance
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin	Give drugs with a small meal or at bed-time
Arthralgia	Pyrazinamide	Aspirin
Itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Anti-histamines
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50 to 75 mg/dL
Major		Stop responsible drug
Skin rash	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop streptomycin, isoniazid, rifampicin, pyrazinamide. Try to identify offending drug by challenging with small doses. Re-introduce other drugs
Deafness, dizziness	Streptomycin	Stop streptomycin. Use ethambutol
Jaundice, hepatitis	Isoniazid, rifampicin, pyrazinamide	Stop isoniazid, rifampicin, pyrazinamide. Use streptomycin and ethambutol. Monitor liver function tests (LFTs). Re-introduce isoniazid, rifampicin, pyrazinamide after LFTs become normal
Visual impairment	Ethambutol	Stop ethambutol
Flu syndrome	Rifampicin	Stop rifampicin
Acute renal failure	Rifampicin	Stop rifampicin
Thrombocytopenia	Rifampicin	Stop rifampicin
Shock	Rifampicin	Stop rifampicin

Isoniazid preventive therapy:

10 mg/kg daily for a period of six months

- Children <6 years who are close contacts of TB patients
- For all HIV infected children
- All TST positive children who are receiving immunosuppressive therapy
- Child born to mother who was diagnosed to have TB in pregnancy

BEDAQUILINE (BDQ)

- Diarylquinoline specifically targets mycobacterial ATP synthase which supplies energy to Mycobacterium.
- Strong bactericidal
- High volume of distribution, extensive tissue distribution, highly bound to plasma proteins and hepatically metabolised by **CYP3A4**
- Has extended half life ,means present in the plasma up to 5.5 months post stopping BDQ
- No cross resistance with first line and second line TB drugs.

Criteria :

1. Adults aged > 18 years having Pulmonary MDR-TB.
2. Females should not be pregnant or should be using effective non hormone based birth control pills .

Dosage :

400 mg a day for 2 weeks, 200 three times a week for 22 weeks

ASSESSING RISK FOR DRUG RESISTANCE

Risk Factors for Resistance	Comments
Failure of retreatment regimen (a second course of treatment after failure, relapse, or default)	Patients who are still sputum smear positive at the end of a retreatment regimen have perhaps the highest drug-resistance rates of any group, often exceeding 80%.
Close contact with a known drug-resistant case	Tuberculosis in close contacts of drug-resistant TB patients is likely to be drug-resistant TB.
Failure of the initial treatment regimen	Patients who fail to become sputum smear negative while on treatment are likely to have drug-resistant organisms. However, the likelihood depends on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout treatment. Thus, a detailed history of drugs used is essential. This is especially true for patients treated by private providers, often with nonstandard regimens.
Relapse after apparently successful treatment	Most patients who relapse have fully susceptible organisms. However, under program conditions, an apparent relapse, especially an early relapse, may, in fact, be an unrecognized treatment failure and thus have a higher likelihood of drug resistance.
Return after default without recent treatment failure	The likelihood of drug resistant TB varies substantially in this group, depending in part on the duration of treatment and the degree of adherence before default.
Exposure in institutions that have drug-resistant TB outbreaks or a high drug-resistant TB prevalence	Patients who frequently stay in homeless shelters, prisoners in many countries, and health care workers in clinics, laboratories, and hospitals can have high rates of drug-resistant TB.
Residence in areas with high prevalence of drug-resistant TB	Drug-resistant TB rates in many areas of the world can be high enough to justify routine drug sensitivity testing in all new cases.

SERUM PROTEINS AND LIPIDS IN TUBERCULOSIS

Lipids are important part of immune system. Cholesterol is involved in membrane functions like phagocystosis and cell growth. Studies have shown that lipids are involved in proliferation cycles that convert lymphocytes into cytotoxic cells, enhance macrophage ability to engulf mycobacterium, its content in lymphocyte is needed for lymphocyte's cytotoxic action. Cholesterol is needed for release of interferon-gamma and TNF-alpha from macrophages that render them efficient killing of mycobacterium.

Various studies have that cholesterol intergral part of cellular immunity, low levels of which has destructive effect on lymphocyte and macrophage. Not only in tuberculosis lipids are found to be reduced in other bacterial infection and sepsis.

Though extact mechanism underlying low serum lipids in sepsis and severe illness is not known , could be due to interaction of cytokines and toxins with lipids and leading to destruction of lipids by peroxidation. Cholesterol and lipoprotein mediate clearance of lipopolysaccharide (produced by bacteria) by detoxification.

During severe infection cytokines produced, causes decrease in the level of cholesterol. Lipoproteins are also involved in clearance of DNA and RNA viruses and also in defence against parasite.

Studies have shown that lipid levels are lower in tuberculosis patients compared to their household contact[35]. Cholesterol supplementation has shown faster bacteriological sterilization of sputum compared to those given placebo[36]. Lipids are also reduced in inflammatory conditions. Cytokines and toxins produces during infection decrease appetite, resulting in weight loss[37].

Cholesterol seems to correlate with severity of infection with lower levels associated with more severe radiological destruction of lung parenchyma and sputum positivity[36,38,41].

It is well established that changes in serum protein occur in response to both acute and chronic infection. In pulmonary TB biochemical abnormality such as low serum albumin, increased bilirubin and ALP are common. Though hypoalbuminemia is not of diagnostic value, they do indicate the severity of infection[39]. With albumin level decrease as the severity of disease increases.

Studies have shown significant lower levels of serum proteins and lipids in patients with tuberculosis and community acquired pneumonia than in contacts and a inverse relationship between radiological extent of infection and HDL levels

Hypoalbuminemia and hypocholesterolemia have shown to improve with treatment and correlate well with recovery from the infection. Hence this could be used to asses the severity of the disease and response to treatment. Hence the aim of the study is to know the prevalence of hypocholestrelemia and hypoalbuminemia in pulmonary tuberculosis patients.

Being a simple non invasive method this could be used to monitor patients on ATT during follow up on treatment course.

Materials and methods

MATERIALS AND METHODS

SETTING

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital (RGGGH), Madras Medical College, Chennai.

ETHICAL COMMITTEE APPROVAL

- Obtained

STUDY DURATION

- This study was conducted over a period of six months.

STUDY POPULATION

- Patients who were admitted with pulmonary tuberculosis to the medical
- Wards at the Institute of Internal Medicine.

SAMPLE SIZE

- Case : 50
- Control : 50

TYPE OF STUDY

- Case-Control study

CASE

Inclusion criteria:

1) Pulmonary tuberculosis
2) Age 20 to 50 years
3) Newly diagnosed

Exclusion criteria:

1) Patients suffering from liver disease
2) Pregnant patients
3) Patients with HIV infection
4) Patients with terminal illness.
5) Any previous anti tuberculous drug treatment
6) Extrapulmonary Tuberculosis

CONTROL

Inclusion criteria:

- Age and gender matched healthy contacts or asymptomatic individuals with no evidence of tuberculosis based on history and clinical examination of 20- 50 years

Exclusion criteria:

1) Any liver disease
2) Pregnancy
3) With HIV infection
4) With terminal illness.
5) Any previous anti tuberculous drug treatment

DATA COLLECTION AND METHODS

On patients who were admitted in RGGGH, Chennai, a case-control study on newly diagnosed smear positive pulmonary tuberculosis patient (case) and with age and gender matched control with no previous or current history of tuberculosis , for period of 6months. Case and control were selected according to the inclusion and exclusion criteria. Detail history taking and examination will be done.

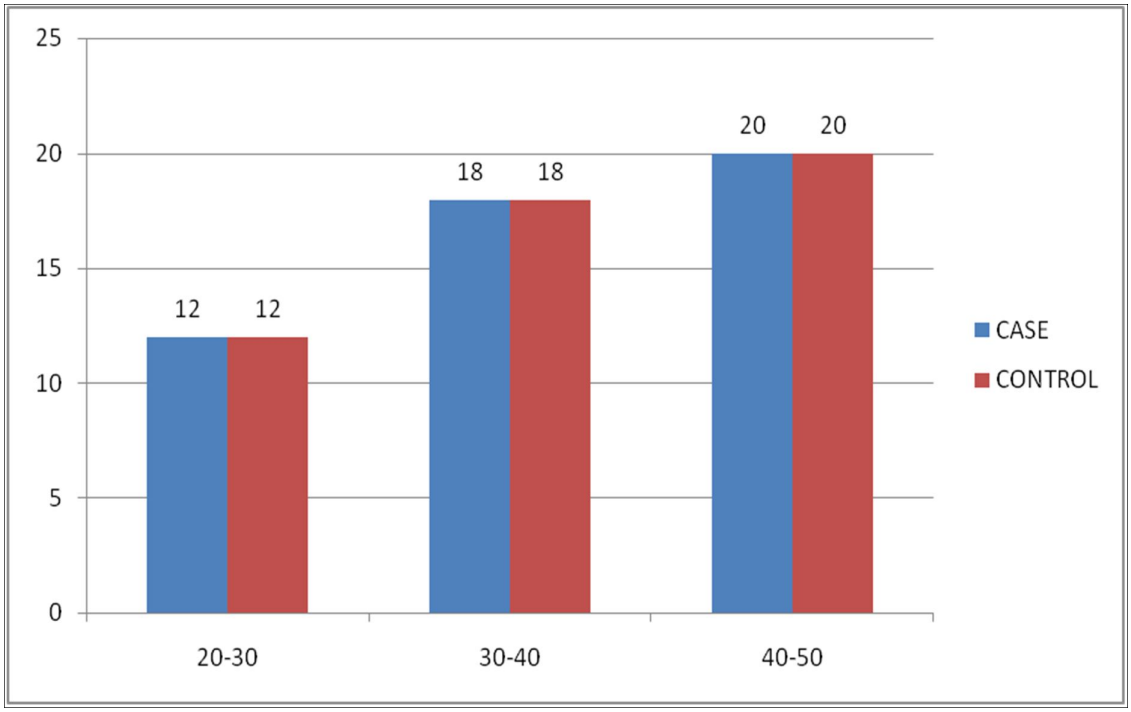
In all patients 3 to 4 ml of venous blood will be collected in a sterile manner in plain red tube for serum protein estimation. And a fasting early morning sample be take for estimation of cholesterol and HDL level.

Observation and results

OBSERVATION & RESULTS

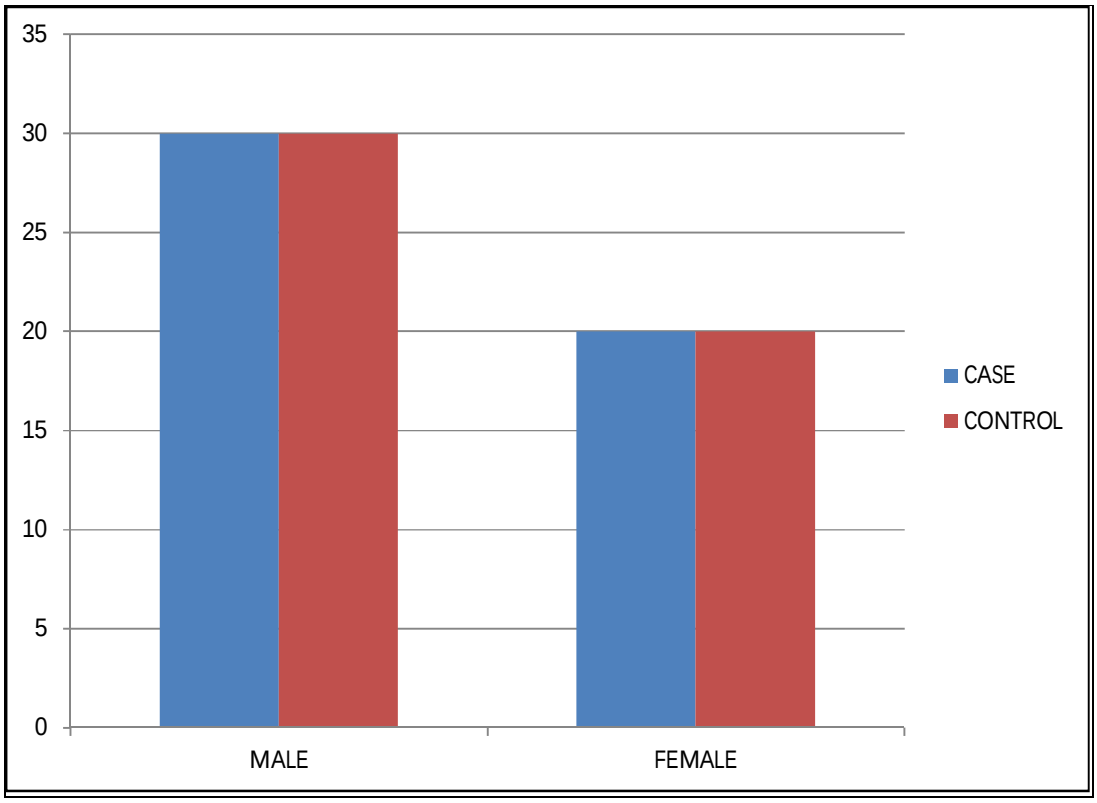
AGE DISTRIBUTION IN CASE AND CONTROL GROUP

AGE DISTRIBUTION		GROUP		Total
		Case	Control	
20-30 Years	Count	12	12	24
	% within group	24.0%	24.0%	24.0%
31-40 Years	Count	18	18	36
	% within group	36.0%	36.0%	36.0%
41-50 Years	Count	20	20	40
	% within group	40.0%	40.0%	40.0%
Total	Count	50	50	100
	% within group	100.0%	100.0%	100.0%



SEX DISTRIBUTION IN CASE AND CONTROL GROUP

SEX	CASE	CONTROL	PERCENT
Male	30	30	60
Female	20	20	40
Total	50	50	100.0



COMPARISION OF LEVELS OF SERUM PROTEIN, ALBUMIN, CHOLESTEROL AND HDL IN CASE AND CONTROL

Group		N	Mean	Std. Deviation	Std. Error Mean	t value	p value
AGE	Case	50	37.46	8.29	1.17	0.012	0.99
	Control	50	37.44	8.15	1.15		
SERUM PROTEIN g/dl	Case	50	5.22	0.73	0.10	15.484**	p<0.001
	Control	50	6.98	0.33	0.05		
ALBUMIN mg/dl	Case	50	2.70	0.42	0.06	16.998**	p<0.001
	Control	50	4.02	0.35	0.05		
CHOLESTEROL mg/dl	Case	50	114.62	22.40	3.17	13.518**	p<0.001
	Control	50	159.40	6.86	0.97		
HDL mg/dl	Case	50	33.14	10.03	1.42	15.819**	p<0.001
	Control	50	58.34	5.13	0.73		

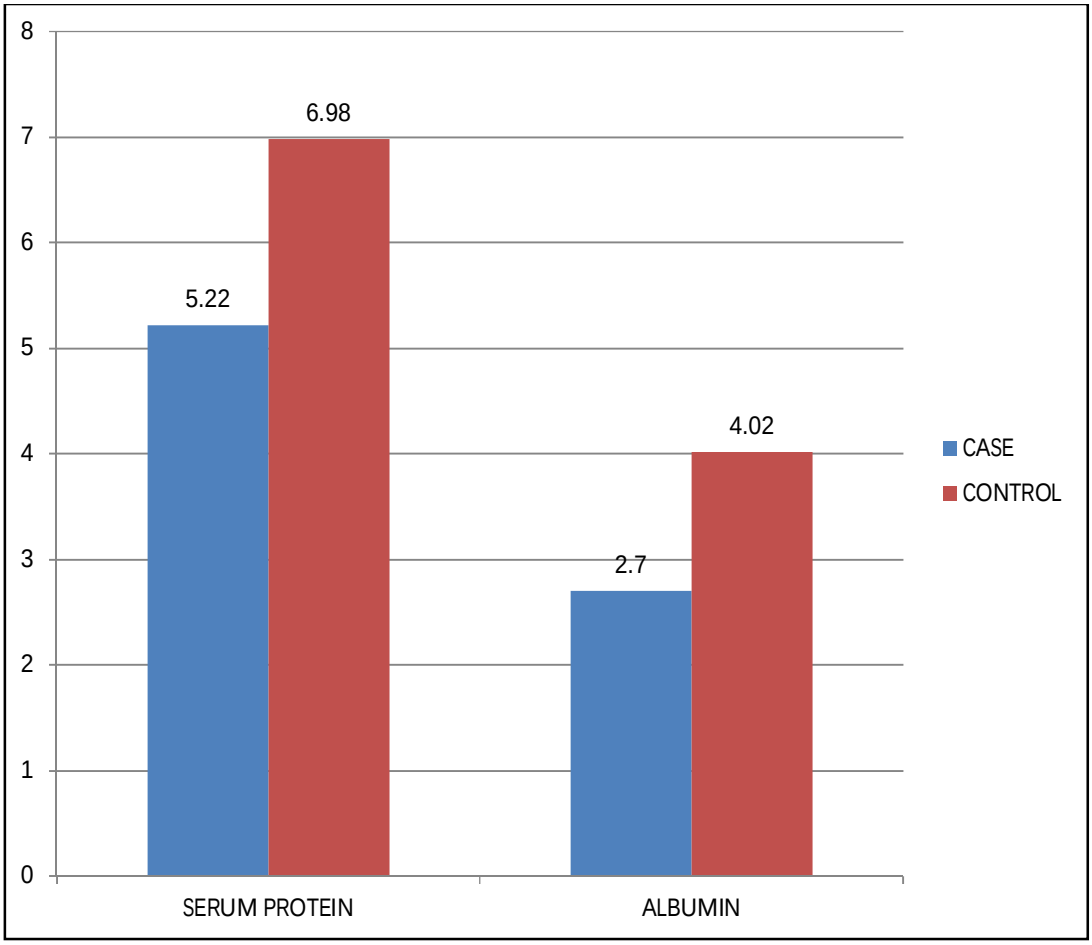
**p<0.001 highly significant

COMPARISION OF SERUM PROTEIN AND ALBUMIN LEVELS BETWEEN CASE AND CONTROL

SERUM PROTEIN g/dl		Group		Total
		Case	Control	
Abnormal	Count	47	3	50
	% within group	94.0%	6.0%	50.0%
Normal	Count	3	47	50
	% within group	6.0%	94.0%	50.0%
Total	Count	50	50	100
	% within group	100.0%	100.0%	100.0%

ALBUMIN mg/dl		Group		Total
		Case	Control	
Abnormal	Count	48	1	49
	% within group	96.0%	2.0%	49.0%
Normal	Count	2	49	51
	% within group	4.0%	98.0%	51.0%
Total	Count	50	50	100
	% within group	100.0%	100.0%	100.0%

MEAN SERUM PROTEIN AND ALBUMIN LEVEL IN CASE AND CONTROL

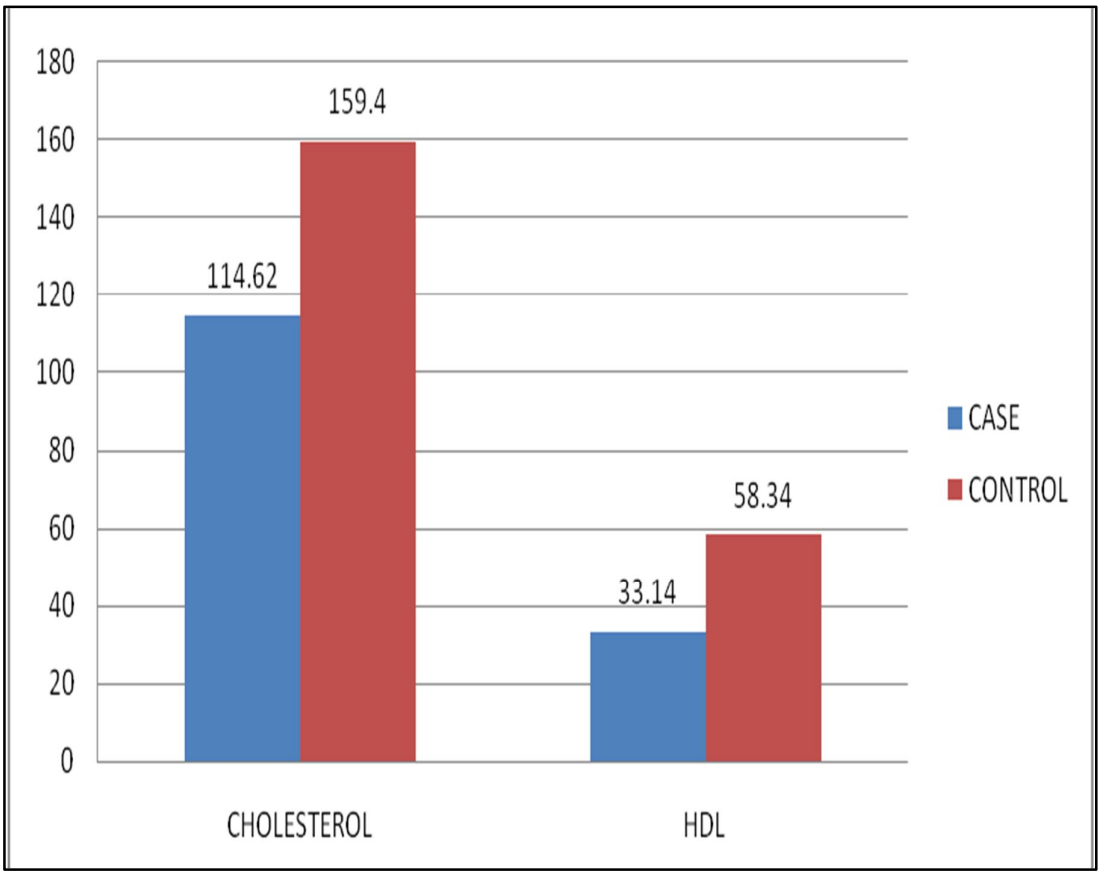


COMPARISION OF SERUM CHOLESTEROL AND HDL LEVELS BETWEEN CASE AND CONTROL

CHOLESTEROL		Group		Total
		Case	Control	
Abnormal	Count	50	50	100
	% within group	100.0%	100.0%	100.0%
Total	Count	50	50	100
	% within group	100.0%	100.0%	100.0%

HDL		Group		Total
		Case	Control	
Abnormal	Count	46	1	47
	% within group	92.0%	2.0%	47.0%
Normal	Count	4	49	53
	% within group	8.0%	98.0%	53.0%
Total	Count	50	50	100
	% within group	100.0%	100.0%	100.0%

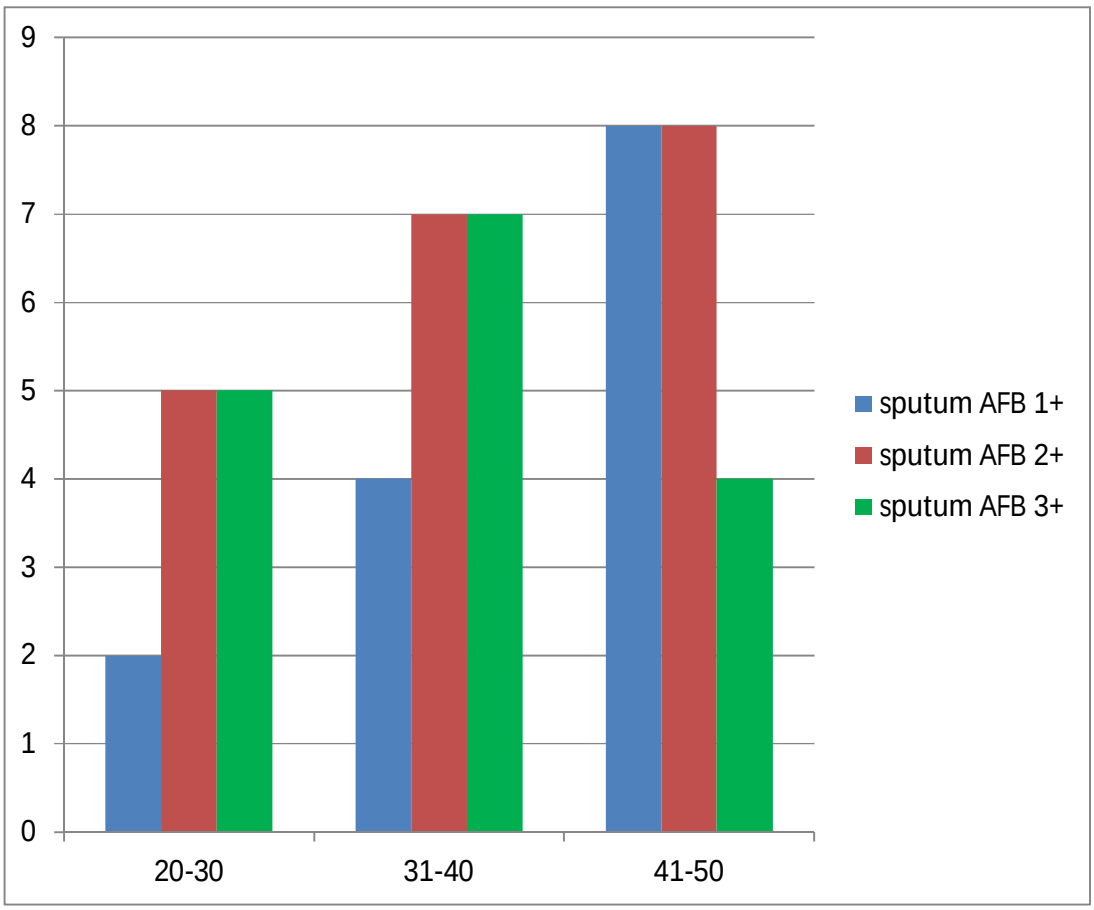
MEAN SERUM CHOLESTEROL AND HDL LEVEL IN CASE AND CONTROL GROUP



AGE DISTRIBUTION OF SPUTUM AFB POSTIVITY IN CASE

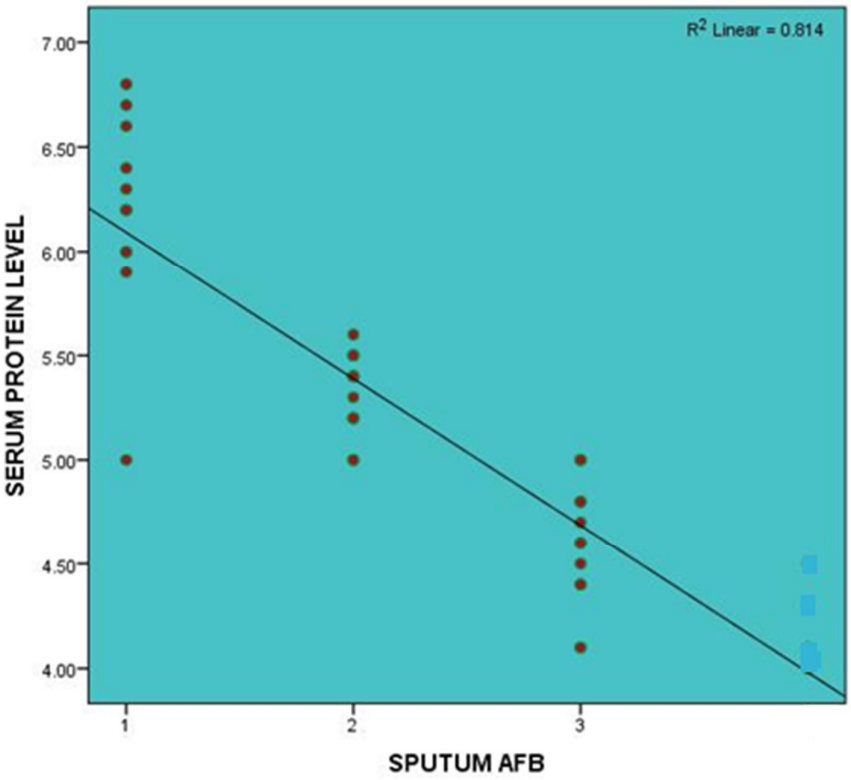
AGE		SPUTUM AFB			TOTAL
		1+	2+	3+	
20-30 Years	Count	2	5	5	12
	% within SPUTUM AFB	16.7%	25%	35.7%	24.0%
31-40 Years	Count	4	7	7	18
	% within SPUTUM AFB	33.3%	36.8%	50%	36.0%
41-50 Years	Count	8	8	4	20
	% within SPUTUM AFB	57.1%	43%	25%	40.0%
Total	Count	14	20	16	50
	% within SPUTUM AFB	100.0%	100.0%	100.0%	100.0%

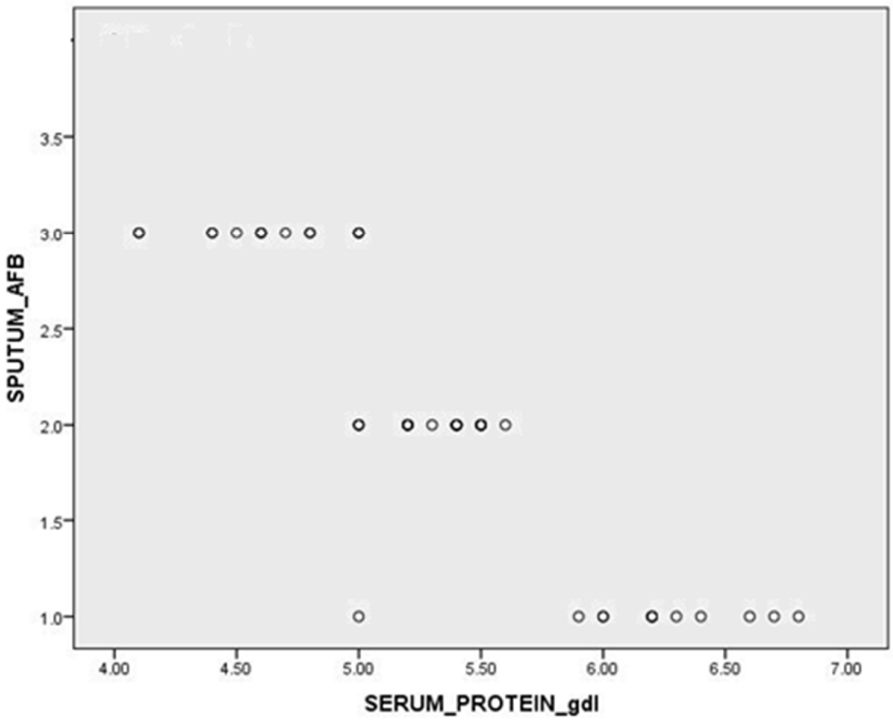
AGE DISTRIBUTION OF SPUTUM AFBPOSTIVITY IN CASE



CORRELATION OF SERUM PROTEIN AND SPUTUM AFB POSTIVITY IN CASE

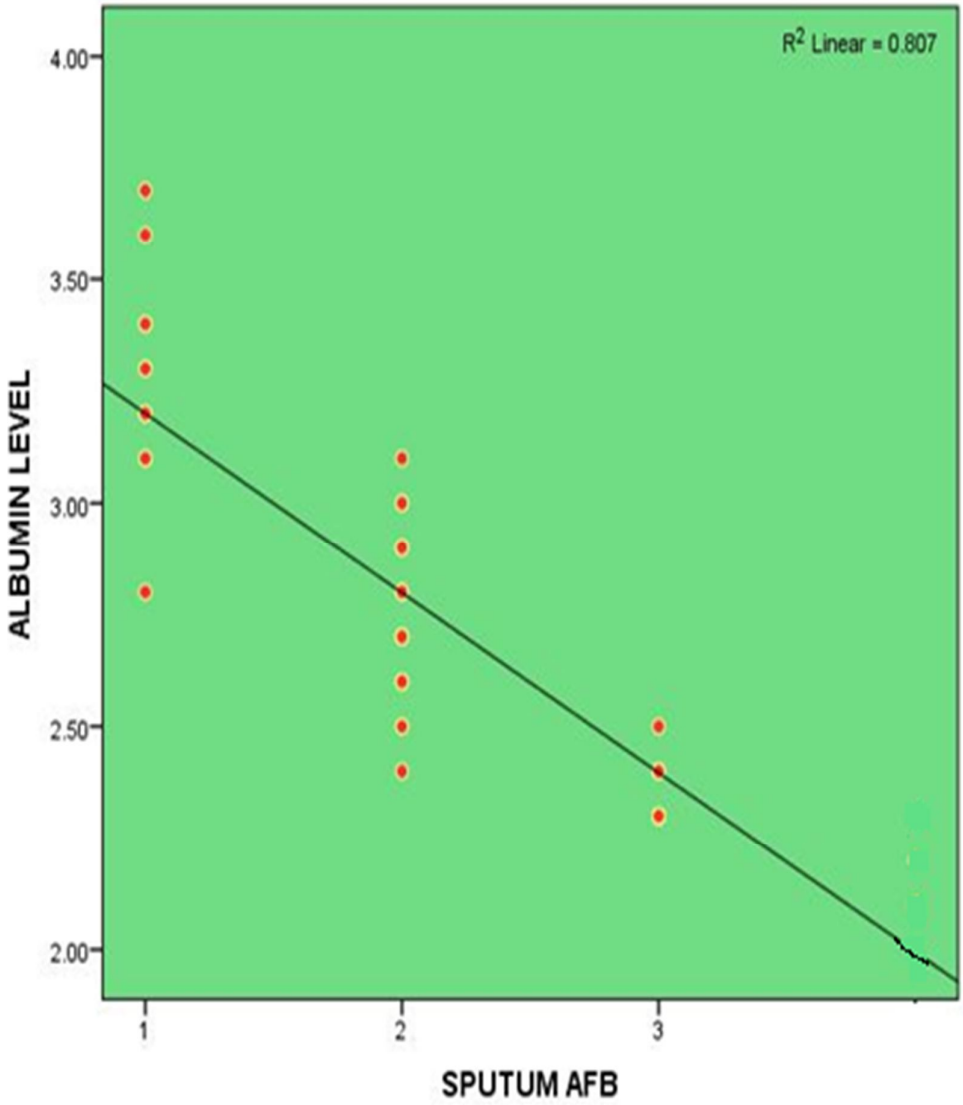
SERUM PROTEIN		SPUTUM AFB			Total
		1+	2+	3+	
Abnormal	Count	11	20	16	47
	% within Sputum AFB	75.0%	100.0%	100.0%	94.0%
Normal	Count	3	0	0	3
	% within Sputum AFB	25.0%	0.0%	0.0%	6.0%
Total	Count	14	20	16	50
	% within Sputum AFB	100.0%	100.0%	100.0%	100.0%


R² Linear = 0.814
SERUM PROTEIN LEVEL
7.00
6.50
6.00
5.50
5.00
4.50
4.00
1
2
3
SPUTUM AFB


SPUTUM_AFB
3.5
3.0
2.5
2.0
1.5
1.0
4.00
4.50
5.00
5.50
6.00
6.50
7.00
SERUM_PROTEIN_gdl

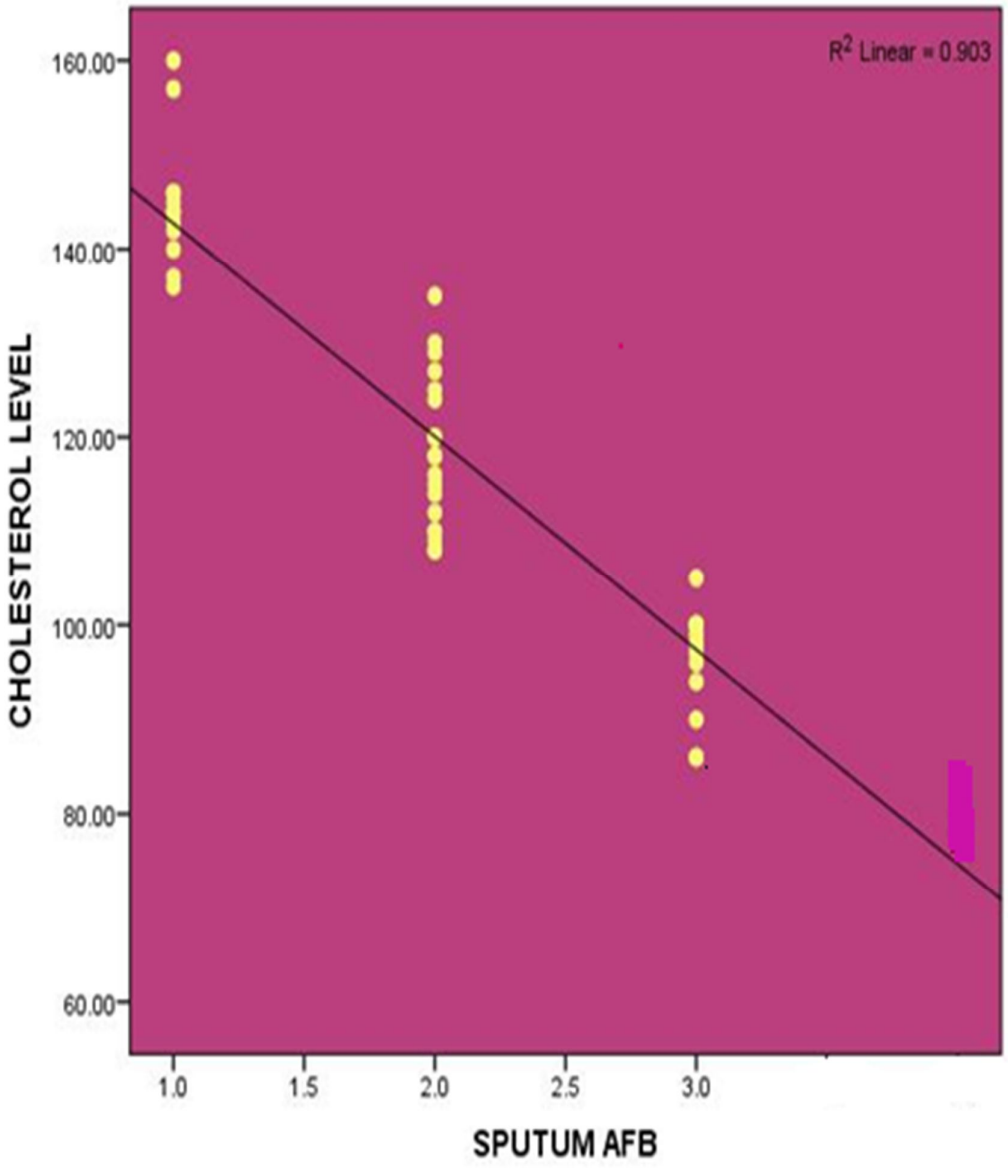
CORRELATION OF SERUM ALBUMIN AND SPUTUM AFB POSTIVITY IN CASE

ALBUMIN		SPUTUM AFB			Total
		1+	2+	3+	
Abnormal	Count	12	20	16	48
	% within Sputum AFB	83.3%	100.0%	100.0%	96.0%
Normal	Count	2	0	0	2
	% within Sputum AFB	16.7%	0.0%	0.0%	4.0%
Total	Count	14	20	16	50
	% within Sputum AFB	100.0%	100.0%	100.0%	100.0%


R^2 Linear = 0.807
4.00
3.50
3.00
2.50
2.00
ALBUMIN LEVEL
1
2
3
SPUTUM AFB

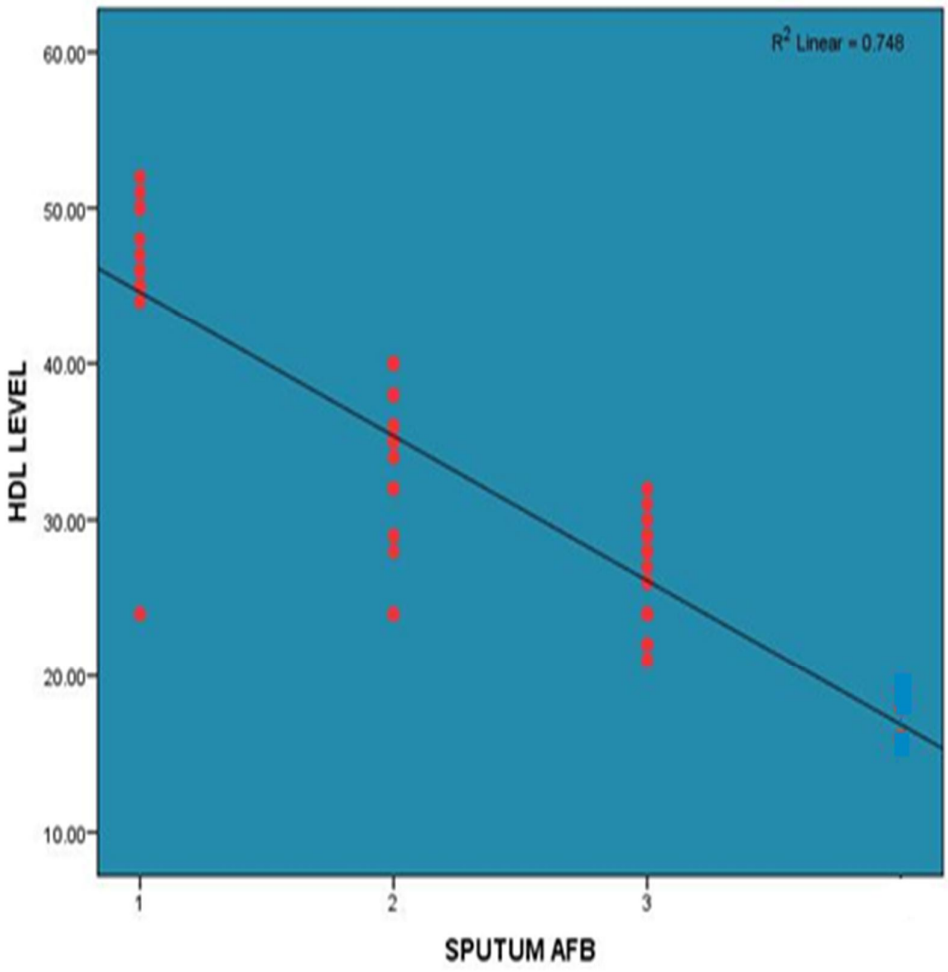
CORRELATION OF SERUM CHOLESTEROL AND SPUTUM AFB POSTIVITY IN CASE

CHOLESTEROL		SPUTUM AFB			Total
		1+	2+	3+	
Abnormal	Count	14	20	16	50
	% within Sputum AFB	100.0%	100.0%	100.0%	100.0%
Total	Count	14	20	16	50
	% within Sputum AFB	100.0%	100.0%	100.0%	100.0%


R^2 Linear = 0.903
160.00
140.00
120.00
100.00
80.00
60.00
CHOLESTEROL LEVEL
1.0
1.5
2.0
2.5
3.0
SPUTUM AFB

CORRELATION OF HDL LEVEL AND SPUTUM AFB POSTIVITY IN CASE

			SPUTUM AFB			Total
			1+	2+	3+	
HDL	Abnormal	Count	10	20	16	46
		% within SPUTUM AFB	66.7%	100.0%	100.0%	92.0%
	Normal	Count	4	0	0	4
		% within SPUTUM AFB	33.3%	0.0%	0.0%	8.0%
Total		Count	14	20	16	50
		% within SPUTUM AFB	100.0%	100.0%	100.0%	100.0%


R^2 Linear = 0.748
60.00
50.00
40.00
30.00
20.00
10.00
HDL LEVEL
1
2
3
SPUTUM AFB

CORRELATION COEFFICIENT OF LEVELS OF SPUTUM AFB AND SERUM LEVELS OF PROTEIN, ALBUMIN, CHOLESTEROL AND HDL IN CASE

		SPUTUM AFB
SERUM PROTEIN g/dl	Correlation Coefficient	-.908**
	Sig. (2-tailed)	p<0.0001
	N	50
ALBUMIN g/dl	Correlation Coefficient	-.934**
	Sig. (2-tailed)	p<0.0001
	N	50
CHOLESTEROL mg/dl	Correlation Coefficient	-.954**
	Sig. (2-tailed)	p<0.0001
	N	50
HDL mg/dl	Correlation Coefficient	-.843**
	Sig. (2-tailed)	p<0.0001
	N	50

RESULTS

AGE DISTRIBUTION:

In our study mean age of case and control is 37.46. In case about 24% patients are between age 20 to 30, 36% patients are between age 31 to 40, 40% patients are between age 41 to 50. Same as in control group.

SEX DISTRIBUTION:

In our study, 60% are males in both case and control group and 40% are females in both case and control group.

MEAN SERUM PROTEIN LEVEL IN CASE AND CONTROL:

Mean serum protein level in case is 5.22 g/dl and in control is 6.98g/dl.

MEAN SERUM ALBUMIN LEVEL IN CASE AND CONTROL:

Mean serum albumin level in case is 2.7g/dl and in control is 4.02 g/dl.

MEAN SERUM CHOLESTEROL LEVEL IN CASE AND CONTROL:

Mean serum cholesterol level in case is 114.62 mg/dl and in control is 159.40 mg/dl.

MEAN SERUM HDL LEVEL IN CASE AND CONTROL:

Mean serum HDL level in case is 33.14 mg/dl and in control is 58.34 mg/dl.

DISTRIBUTION OF SPUTUM AFB IN CASES (AGE WISE):

Sputum AFB 1+ is about 16.7% in age group 20-30yrs, 33.3% in age group 31-40 yrs, 57.1% in age group 41-50 yrs. Sputum AFB 2+ is about 25% in age group 20-30yrs, 36.8% in age group 31-40 yrs, 43% in age group 41-50yrs. Sputum AFB 3+ is about 35.7% in age group 20-30yrs, 50% in age group 31-40 yrs, 25 % in age group 41-50 yrs.

DISTRIBUTION OF SPUTUM AFB IN CASE (SEX WISE):

In males sputum AFB 1+ is positive in 8, 2+ in 12 and 3+ in 9. In females sputum AFB 1+ is positive in 8, 2+ in 8 and 3+ in 5 .

COMPARISION OF SERUM LEVELS OF PROTEIN, ALBUMIN, CHOLESTEROL AND HDL BETWEEN CASE AND CONTROL:

In our study, we compared the levels of the above said parameters between case and control. p value was found to be 0.99 in comparison of age distribution between case and control which is insignificant. p value is of <0.001 in comparision of serum levels of protein, albumin, cholesterol and HDL between case and control group which is highly significant.

CORRELATION OF SERUM LEVELS OF PROTEIN, ALBUMIN, CHOLESTEROL AND HDL WITH SPUTUM AFB POSTIVITY IN CASE:

In our study, correlation of sputum AFB positivity with above mentioned value has shown as the sputum positivity increases the measured serum levels of the values decreases, indicating as the bacterial load increases the values decrease. p value on individual correlation of serum levels of protein, albumin, cholesterol and HDL and sputum positivity (from 1+ to 3+) is highly significant <0.0001 [33,12,41].

Discussion

DISCUSSION

In this study 50 patients of newly diagnosed sputum positive pulmonary tuberculosis diagnosed at RGGGH were selected and their serum levels of protein, albumin, cholesterol and HDL was compared with 50 age and gender matched controls. Case and control were selected as per the inclusion and exclusion criteria. They were subjected to detail clinical examination.

p value obtained by this comparison and with correlation of the serum protein, albumin cholesterol and HDL levels with sputum positivity in case was found to be highly significant.

Sample size:

In this case control study, 50 were cases(newly diagnosed pulmonary tuberculosis) and 50 control were included. In Ofor. I.B. et al study 16 was newly diagnosed TB, 20 on ATT for 3 months, 20 on ATT for 6 months and 20 were healthy volunteers as control[34]. In Laxmikant Chavan[33] study 100 patients of newly diagnosed pulmonary and extrapulmonary TB were included.

AGE:

In this study, mean age was 37.46 years in case and 37.44 years in control. .In Laxmikant Chavan study mean age of adults less than 40 years was 32.71 and mean age above 40 years was 67.57 years. Ofor. I.B study subjects included were of age group 15-60 years.

SEX:

In this study, 30 were male and 20 female in both case and control.

Comparision of serum levels of protein, albumin, cholesterol and HDL in case and control.

p value was found to be significant in comparison of above mentioned variables between case and control. The value did correlate with sputum AFB positivity in this study , with p value being significant[12,41] . This is supported by Laxmikant Chavan study where the levels of serum proteins correlated with severity of infection by sputum AFB and radiological extent of the disease.

Conclusion

CONCLUSION

This study showed that serum levels of protein, albumin, cholesterol and HDL was low in case compared to control and that these values were in decreasing trend as the sputum positivity increased from 1+ to 4+. Indicating that as the bacterial load increases and severity of infection increased these values decreased. Hence they may be play significant role in monitoring tuberculosis patients on ATT to look for improvement in these serum levels as the bacterial load decreases and sputum becomes negative. And to may add a benefit in looking for response to treatment in these patients with improvement both clinically and biochemically.

Limitations

LIMITATIONS

- Sample size being less in the view of the load of this disease in our country.
- Extra –pulmonary TB not been included.
- Long term follow up of these patients to look for improvement in these parameters with treatment.

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Annexures

PROFORMA

1. Name:

2. Age/Sex:

3.IP.No.:

4.Diagnosis:

5.Occupation:

COMPLAINTS:

PAST HISTORY:

1. DM/SHT

2. CLD

3. TB

4. HIV

5. CHRONIC RENAL FAILURE

6. CAD

PERSONAL HISTORY:

Alcoholic/ smoker:

VITALS:

BP:

PULSE RATE:

EXAMINATION:

General examination

1) Conscious / Oriented
2) Pallor / Icterus
3) Pedal Edema
4) Lymphadenopathy

Systemic examination

Cardiovascular system:

Respiratory system:

Abdomen:

CNS:

INVESTIGATIONS

Total protein:

Albumin:

Globulin:

Lipid profile:

Total cholesterol

HDL

INFORMATION SHEET

We are conducting a study on **"A CASE-CONTROL STUDY ON SERUM PROTEIN, CHOLESTEROL AND HDL LEVELS IN PULMONARY TUBERCULOSIS PATIENTS."** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your co-operation to undergo relevant investigations as per need may be valuable to us.

The purpose of this study is to study the prevalence of hypoalbuminemia and hypocholestrelemia in pulmonary tuberculosis patients.

We are selecting certain cases and if you are found eligible, we would like to perform extra tests and you will be subjected to a non invasive procedure like estimation of serum protein, cholesterol and HDL level which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature/left thumb impression of Participant

PATIENT CONSENT FORM

Study Detail : **"A CASE-CONTROL STUDY ON SERUM PROTEIN, CHOLESTEROL AND HDL LEVELS IN PULMONARY TUBERCULOSIS PATIENTS."**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

In Patient Number :

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. o

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. o

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. o

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. o

e) I hereby consent to participate in this study. o

f) I hereby give permission to undergo detailed clinical examination and relevant investigations as required. o

Study Investigator's Name Signature/thumb impression

Study Investigator's Name:

Dr. K.TEENA Patient's Name and Address:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Teena.K.
Post Graduate in M.D.(General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Teena.K.

The Institutional Ethics Committee has considered your request and approved your study titled **"A CASE – CONTROL STUDY ON SERUM PROTEIN, CHOLESTEROL AND HDL LEVELS IN PULMONARY TUBERCULOSIS PATIENT" - NO.10022017**

The following members of Ethics Committee were present in the meeting hold on **07.02.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.S.Suresh, MS., Prof.of Surgery, MMC, Ch-3	: Member
5.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
6.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

URKUND

Urkund Analysis Result

Analysed Document: Final main thesis.docx (D30486038)
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Sources included in the report:

Instances where selected sources appear:

0

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"A CASE- CONTROL STUDY ON SERUM PROTEIN, CHOLESTEROL AND HDL IN PULMONARY TUBERCULOSIS PATIENTS"** of the candidate **DR. TEENA .K** with registration Number **201511024** for the award of **M.D** in the branch of **GENERAL MEDICINE.** I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **0 percentage** of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

MASTER CHART

CASE

S.No.	AGE	SEX	SPUTUM AFB	SERUM PROTEIN g/dl	ALBUMIN g/dl	CHOLESTEROL mg/dl	HDL mg/dl
1	40	M	1+	6	2.8	140	44
2	35	M	2+	5	2.5	109	32
3	42	F	2+	5.5	2.8	110	36
4	24	M	3+	5	2.5	100	26
5	49	F	1+	4.5	2.2	80	18
6	25	F	2+	5.6	2.9	120	35
7	34	F	3+	4.1	2.3	98	21
8	36	M	1+	5.9	3.2	143	50
9	44	M	2+	5.2	2.4	116	38
10	26	M	2+	5.3	2.5	130	40
11	47	M	1+	4.1	2.3	78	16
12	38	F	3+	4.5	2.3	100	22
13	40	M	2+	5.4	2.6	118	32
14	45	F	1+	6.4	3.3	136	48
15	33	M	2+	5.5	2.9	124	36
16	25	M	2+	5.4	2.8	112	38
17	50	F	2+	5.2	2.9	108	34
18	21	F	3+	4.6	2.4	94	28
19	43	M	1+	6.3	3.1	144	45
20	38	M	2+	5.2	3.1	108	28
21	48	F	2+	5.4	2.6	127	38
22	29	F	3+	5	2.3	86	24
23	35	M	1+	5	3.4	142	24
24	42	M	2+	5	2.6	115	24
25	41	F	2+	5	3	129	24

S.No.	AGE	SEX	SPUTUM AFB	SERUM PROTEIN g/dl	ALBUMIN g/dl	CHOLESTEROL mg/dl	HDL mg/dl
26	25	M	1+	6.2	3.2	144	45
27	37	M	3+	4.1	2.3	98	27
28	47	F	1+	6.2	3.2	137	46
29	25	M	3+	4.4	2.4	99	29
30	33	F	2+	5.4	2.7	110	35
31	45	M	1+	6	3.3	145	47
32	39	M	3+	4.6	2.3	97	29
33	50	M	3+	4.7	2.3	100	32
34	29	F	3+	4.8	2.4	105	31
35	31	F	1+	6.6	3.7	154	50
36	38	M	2+	6.7	3.5	156	49
37	42	M	3+	5	2.3	86	24
38	49	F	3+	4.1	2.2	78	16
39	37	F	2+	5.5	2.8	120	40
40	42	F	1+	6.7	3.6	160	52
41	24	M	2+	5.4	2.7	118	29
42	49	F	2+	5.5	2.7	114	35
43	28	F	1+	6.2	3.1	146	46
44	36	M	3+	4.3	2.1	80	19
45	29	M	2+	4	2	78	18
46	31	M	3+	4.8	2.3	90	30
47	39	M	3+	4.6	2.3	96	22
48	45	M	2+	6.7	3.6	158	52
49	46	M	1+	6.8	3.7	157	51
50	47	M	3+	4.4	2.4	100	28

CONTROL

S.No.	AGE	SEX	SPUTUM AFB	SERUM PROTEIN g/dl	ALBUMIN g/dl	CHOLESTEROL mg/dl	HDL mg/dl
1	25	M	-	6.6	3.6	155	50
2	36	M	-	6.7	3.8	155	50
3	31	F	-	7.1	4.2	155	50
4	42	F	-	7.2	4	155	58
5	26	M	-	6.9	4.5	155	49
6	29	M	-	6.6	3.5	155	50
7	21	F	-	7	3.8	155	60
8	33	F	-	7.2	3.9	155	61
9	44	M	-	6.9	4.2	155	55
10	35	M	-	7.6	3.7	155	59
11	25	F	-	7.5	4.4	155	62
12	34	F	-	6.7	4.2	155	65
13	38	M	-	6.8	4.7	155	67
14	42	M	-	7	4.3	155	58
15	39	M	-	7.1	4.5	155	60
16	38	F	-	7.3	3.7	155	58
17	37	F	-	6.9	3.8	155	62
18	30	F	-	7.4	4	155	64
19	26	M	-	7	4.1	155	52
20	38	M	-	6.9	3.9	155	55
21	39	M	-	7.2	4.4	155	56
22	47	M	-	6.7	4.2	155	62
23	48	F	-	6.9	3.8	155	64
24	48	M	-	7.1	3.6	155	59
25	49	F	-	6.5	3.6	155	55

S.No.	AGE	SEX	SPUTUM AFB	SERUM PROTEIN g/dl	ALBUMIN g/dl	CHOLESTEROL mg/dl	HDL mg/dl
26	28	M	-	7.8	4.5	165	57
27	25	M	-	7.1	4	155	56
28	33	M	-	6.7	4.3	160	60
29	48	F	-	6.9	3.7	162	66
30	29	F	-	7.2	3.8	164	70
31	41	F	-	7.1	3.6	180	53
32	45	M	-	6.6	4.2	159	56
33	50	M	-	6.9	4.7	167	59
34	26	F	-	7.8	4.9	154	60
35	49	F	-	6.7	4	179	52
36	24	M	-	6.9	3.6	154	60
37	47	M	-	6.6	3.4	158	64
38	43	F	-	7.5	3.8	157	65
39	45	F	-	7.4	4.2	174	68
40	41	M	-	7.2	4.3	167	56
41	44	M	-	6.6	4.5	156	55
42	46	M	-	6.7	4.2	161	57
43	50	F	-	6.8	4.2	165	62
44	36	M	-	7.1	4.1	154	63
45	36	M	-	7	3.9	172	57
46	35	M	-	6.5	3.7	173	59
47	42	F	-	6.5	3.9	165	55
48	40	M	-	6.6	3.9	163	50
49	31	M	-	7.1	3.7	165	61
50	38	M	-	6.7	3.5	166	55